Thoracic Surgery

Cervical, Thoracic and Abdominal Approaches

Claudiu E. Nistor · Steven Tsui · Kaan Kırali · Adrian Ciuche · Giuseppe Aresu · Gregor J. Kocher
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Preface

There has been tremendous progress in general thoracic surgery over the last decade with significant advances in surgical techniques and instrumentation. These have meant that more patients are undergoing thoracic surgical treatment with less accompanying morbidity and mortality. The purpose of this work is to provide an up-to-date account of these advances by grouping chest surgery and border surgery according to an anatomical approach. Hopefully, this work will aid surgeons in training, practicing surgeons as well as surgical trainers who are eager to improve their surgical knowledge.

Expert surgeons from all over the world have contributed to this first edition in an attempt to approach and expose, through their own experience, the surgical techniques in different pathologies encountered in thoracic surgery.

Without claiming that this book covers all the techniques of chest surgery, we hope that we have achieved a modern orientation regarding the applicability of these techniques.

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Cambridge, UK — Giuseppe Aresu
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General Aspects of Thoracic Surgery

Claudiu E. Nistor, Adrian Ciuche, and Ecaterina Bontaș

Key Points

- Inventor of human laparoscopy and thoracoscopy is Hans Christian Jacobaeus in 1910.
- Da Vinci robotic system includes three main components: the surgeon's console (the master component), 3D high-definition vision system and the peripheral effector device (slave component).
- VATS offers an excellent visualization of anatomical structures of thoracic inlet and has been introduced in the diagnosis and treatment of Pancoast tumors.

Definitions

Presently, development of videoendoscopic technology and endosurgical procedures produced a rapid expansion of mini invasive surgery in all surgical disciplines, including thoracic surgery.

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Endoscopic surgery is the result of natural evolution of endoscopy, which has progressed through over the past 25 years and has now achieved a complex range of interventions: laser resections, stents, insertions of intrabronchial valves, etc.

This type of surgery aims to achieve diagnostic and therapeutic goals same to open surgery, using minimal access to different body compartments: serous cavities (pleura, pericardium, peritoneum), mediastinum, and retroperitoneal space.

Thoracic mini invasive surgery has gone through successive stages of evolution, from thoracoscopy performed for the first time by Hans Christian Jacobaeus in 1910, to thoracoscopic and video-assisted surgery nowadays [1–4]. Nowadays, an impressive variety of thoracic mini invasive surgical interventions can be performed for the diagnosis and therapeutic purposes, in case of pleural, pulmonary and mediastinal pathology.

Initially, thoracoscopy was performed in the various ways, using either a cystoscope (Hans Christian Jacobaeus in 1910) or a bronchoscope, or a rigid dedicated instrument called thoracoscope. With these devices, surgeons or pneumologists performed minor interventions specifically focused on the diagnosis of pleural diseases.

Subsequently, Fabri and Parmeggiani [5] reported the use of thoracoscopy for the

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evaluation of pleural effusions [5], and later in 1943 Fourestier and Duret published three cases of malignant pleurisy diagnosed by pleuroscopy [6].

Goetz [7] performed the first thoracic denervation (nonselective thoracoscopic sympathectomy).

In 1952, Hopkins introduces the rod-lens system, where long lenses are separated by small airspaces [8].

Between 1989–1990 Cuschieri developed the multipuncture thoracoscopy system, realizing in 1990 the first thoracoscopic esophageal myotomy [9].

Since 1990, thoracoscopy has improved extensively, so that Landreneau, Cuschieri, Marescaux have contributed to the expansion of indications and the development of technical possibilities [10–13]. The introduction of video technology in thoracoscopic interventions has revolutionized this type of surgery by simultaneously viewing the operator field by multiple people, allowing them to participate in surgery, similar to classical thoracic procedures. Since then, video thoracoscopy has exploded virtually all over the world, accompanied by the emergence of guidelines and the standardization of terms used. At the same time, a clear distinction was made between thoracic surgery performed by video equipment and "medical" thoracoscopes used for diagnostic purposes only.

The concept of mini invasive thoracic surgery (Minimally Invasive Thoracic Surgery or Minimal Access Thoracic Surgery) defines the totality of major thoracic surgeries that uses video capture and playback system, that can be performed either by small thoracoscopic thoracic wall holes or by associating at these orifices a mini access thoracotomy.

The advantages of mini invasive surgery transformed it as a method of choice in the diagnosis and treatment of numerous pleural, pulmonary or mediastinal disorders. The introduction of mini invasive surgical techniques in medical practice allowed the giving up to the classical thoracotomies for diagnostic purposes, while ensuring the premise of an early and effective treatment.

The essential attribute of thoracoscopic surgery is to reduce trauma of the access path without compromising the right exposure of operator field.

The postoperative recovery and convalescence of the patient are shortened, thus achieving rapid socio-professional reemployment. The overall cost of hospitalization decreases a lot, and classical postoperative complications are lower. Surgical stress caused by mini invasive surgery compared to classical techniques is lower, postoperative pain is minimal, and the need for analgesics and narcotics is greatly reduced. There is no need to neglect the aesthetic and functional advantages.

Also, magnification of the image allows the observation of anatomical details and a more precise technique.

Many high-tech innovations have been introduced into medical practice and especially surgical. Surgical thoracic pathology is no exception, providing guidelines for applying virtual reality technology to thoracoscopic surgery. These technical developments have found applicability and have been fully integrated into the development of surgical robotic systems.

The first surgical robots were PUMA 560 used in 1985 to place a cerebral biopsy needle under CT and PROBOT [14], developed by Imperial College London and used in 1988 in prostate surgery [15, 16].

The first commercial surgical robotic systems were developed by Intuitive Surgical with the introduction of da Vinci (da Vinci Surgical System) and Computer Motion with AESOP and the ZEUS robotic surgical system. With the purchase of Computer Motion by Intuitive Surgical in 2003, the ZEUS system was not marketed anymore [15, 16].

Developing by Intuitive Surgical Inc. of the robotic system incorporating both robotic-assisted vision and robotic assisted surgical instruments has allowed the use of this technology in the field of thoracic surgery.

Original robotic system of da Vinci system was built and funded under a grant supported by the Defense Advanced Research Projects Agency (DARPA) and NASA (National

Aeronautics and Space Administration) with the intention of building a telesurgical robot for conducting remote surgical interventions in various theaters of military operations in the world or cosmic space (on other planets, orbital stations). The patent of this robot was purchased by Intuitive Surgical, Mountain View, California with the aim to develop mini invasive surgery. The first robotic surgery was conducted in Columbus, Ohio at The Ohio State University Medical Center under the direction of Professor Dr. Robert E. Michler, chief of the cardio-thoracic surgery department. The newest da Vinci system is da Vinci HD SI marketed since April 2009 [15–17].

Da Vinci robotic system includes three main components (Figs. 1 and 2): the surgeon's console (the ***master component***), 3D high-definition vision system and the peripheral effector device (***slave component***) consisting of 4 arms controlled by the surgeon (one for room control and three for the manipulation of mini invasive instruments) [17–19].

Articulated surgical instruments are mounted on the robot arms and inserted into the chest cavity through cannula. The endoscopic camera used in this system provides true stereoscopic images transmitted to the surgeon's console, allowing surgeon to visualize detailed high-definition 3D aspects of the anatomical structures (Fig. 2) [19].

The main technical advantages offered by Da Vinci robotic system are: master-slave control of surgical instruments, the possibility of freezing motion or recalculating the movements of surgical instruments. Consequently, accuracy and precision of surgical gestures represent the main benefit of this technology, which thus finds its applications especially in surgical interventions requiring dissections and meticulous vascular reconstruction [20, 21].

This robotic system allows thoracic surgeon to apply the classical surgical technique at level of computerized console and transfer it to the operator field by simultaneous endosurgical movements of robotic arms including mini invasive surgical instruments (Fig. 3) [17]. In addition, the robotic wrist and joint of surgical instruments allow for a complex game of motion for surgical instruments tip, allowing dissections in deepest areas of the thoracic cavity.

There are also some limitations of the system, which may affect the surgeon's dexterity and may increase the difficulty of surgery. These limits are generated, on the one hand, by ***large dimensions of surgical instruments*** due to their complexity which allows their movements to reach seven degrees of freedom inside

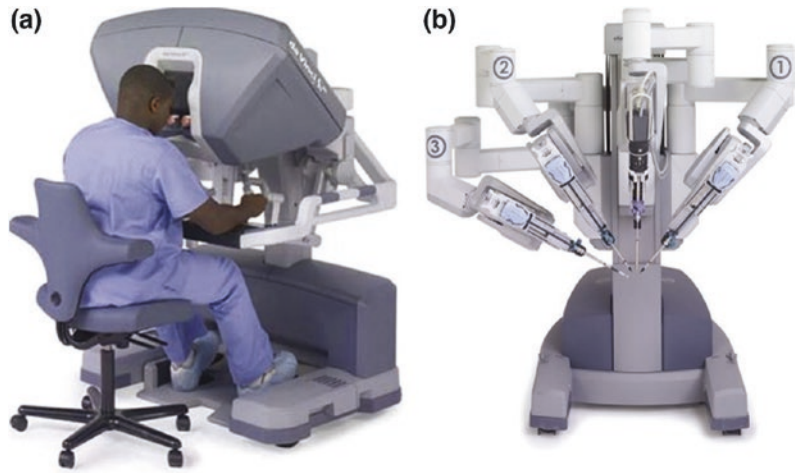


Fig. 1 The three components of da Vinci robotic system: **a** Surgeon console (the master component); **b** The slave component (the peripheral effector device) formed from fours arms. From [17] with permission

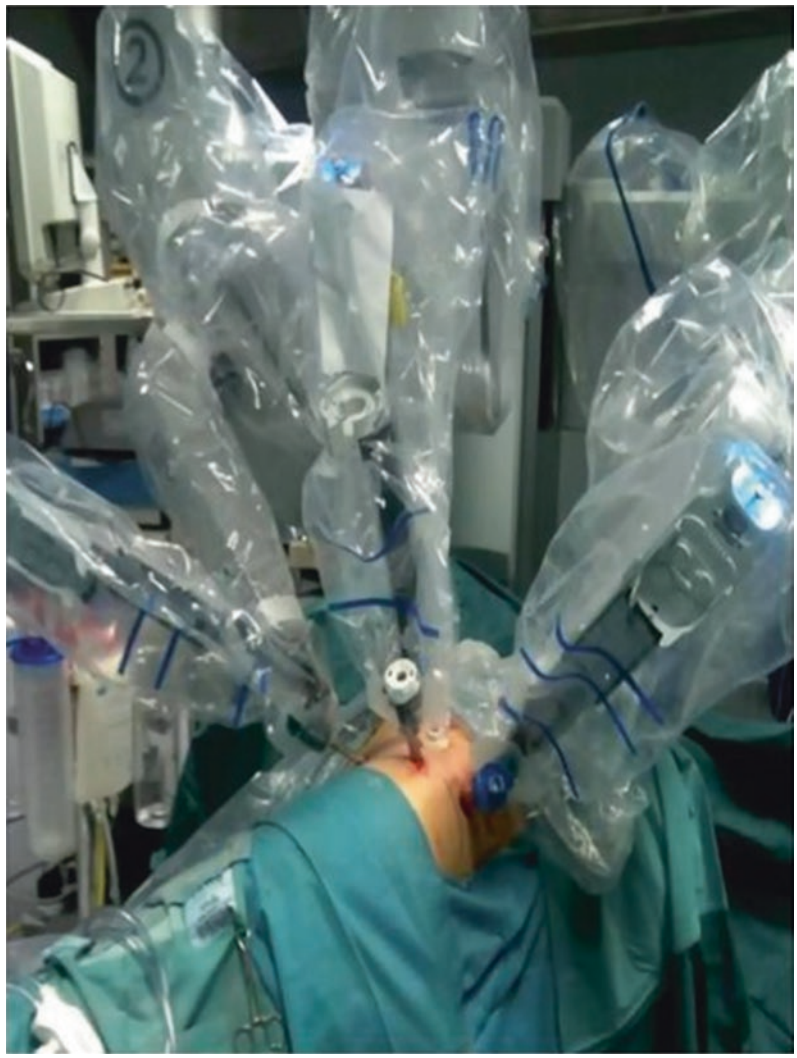


Fig. 2 Da Vinci Si® robotic surgical system docked. From [19] with permission

Fig. 3 Articulated robotic instrument. From [17] with permission

the thoracic cavity and, on the other hand, to the ***lack of tactile sensation*** (the disadvantage of mini invasive surgery in general) and ***tactile feedback*** (the disadvantage of robotic surgery in particular), which affects surgeon's ability to judge the degree of tension applied during ligation maneuvers or surgical sutures. With regard to the first aspect of limitation imposed by size of surgical instrumentation, an improvement in the visualization and efficiency of surgical movements can be achieved by placing the trocars as judicious as possible in the thoracic

cavity, allowing an optimal working angle *between* (1) the plan of approached lesion, (2) the surgical instruments used and (3) the endocamera providing the virtual image of the operator field. With regard to the second aspect, a new technology called ***haptic technology*** is now being developed, which is a technology of tactile feedback by the user (surgeon) vibrations, pressures or movements that simulate the touch of virtual objects. These systems are developed to use a haptic interface for 3D virtual models to generate a virtual experience for real interactive models (patient's anatomical structures).

The first surgical robot incorporating force feedback is SOFIE (Surgeon's Operating Force-feedback Interface Eindhoven), developed by Eindhoven University of Technology in 2010, which compared to the da Vinci system is more compact, adjusts automatic changes to position of surgical table, without the necessity of reconstruction of surgical arms.

Moreover, a recently developed medical innovation is the ***telepresence*** by creating a central control station that practically allows surgeons to perform remote surgery without being physically present in the operating room. This technical achievement allows surgeons experts from some top surgical areas to operate virtually in any corner of country or world without moving from the command point. Thus, remote mini invasive thoracic surgery (mini invasive telesurgery) can be performed by assisting the surgeons directly performing the surgery and surgical interventions by means of the robots mounted on patient by medical staff at that location and handled from a distance by surgeons in the control center (telerobotics).

Robotic surgery has demonstrated feasibility over years in general thoracic surgery especially for lobectomies, esophagectomy, thymus surgery (myasthenia gravis), anterior and visceral mediastinal tumors, and other surgical procedures involving difficult vascular dissection, with net advantages over classical surgical interventions as short hospitalization time, reduced intensity of postoperative pain, better respiratory function and rapid socio-professional reintegration [22, 23].

In mini invasive surgery of pleural space, robotic surgery was applied mainly in spontaneous pneumothorax surgery (by performing limited non-anatomical resections of pulmonary parenchyma, emphysema bubbles ligation, application of chemicals for chemical pleurodesis) and in pleuro-pericardial cystic surgery [24].

The use of robotic surgery will develop and find applications in all surgical fields and in many interventions for the thoracic cavity due to the mini invasive character and the precision of surgical gestures.

As robotic surgery experience is evolving, its disadvantages will become less important and benefits will be much better outlined and defined. Despite disadvantages such as cost-effectiveness compared to other non-invasive robotic interventions, the development of robotic surgery applications and engaging as many surgeons as possible in its study and practice will result in better trained surgeons for new technologies and able to discover new techniques and guidelines with a favorable impact on the treatment of patients.

Progress in thoracic surgery is closely related to the emergence and development of ***anesthesia***. Presently, patients are admitted to the surgery in severe condition with multiple associated risk factors and conditions, with localizations, or in stages where, a few decades ago, the surgeon did not dare to think of operating them. Moreover, modern resources of investigation of thoracic pathology (e.g. fibrobronchoscopy, computed tomography, magnetic resonance, cardiac catheterization) sometimes require anesthetic techniques, which in turn bring new and useful elements to the anesthetist in perioperative period.

The long way of anesthesia from thoracic pulmonary surgery had began at the end of 19th century when the first positive ventilation flap was used to remove a thoracic parietal tumor; and went through all developmental stages of anesthesia, to differentiate during last four decades as a special subspecialty. Use of double-lumen endotracheal tube and separate ventilation of the lungs, use of intraoperative fibrobronchoscopy, use of special ventilation

techniques during anesthesia as positive ventilation with pressure support, continuous positive airway pressure (CPAP) on the operated lung, positive end-expiratory pressure (PEEP), high frequency jet ventilation and so on, with combined loco-regional and general anesthetic techniques, are just a few examples of the anesthetist's techniques which today allow for extensive and long-lasting interventions, even in extremely delicate areas such as tracheal surgery, esophagus or mediastinum with favorable post-operative progression and good prognosis.

Thoracoscopic surgery is generally performed under general anesthesia with selective endotracheal intubation. Patients who can not support general anesthesia, endotracheal intubation (with general altered status or poor respiratory function), can have local anesthesia with sedation.

The variants of anesthesia practiced in mini invasive thoracic surgery are:

Local anesthesia is currently used for minor interventions, such as drainage of pleural effusions, pleural biopsy or pleurodesis with talc, in the form of local anesthesia with xylene or marcaine or bupivacaine, in which is made a generous infiltration of skin, subcutaneous tissue, intercostal space and of the adjacent pleura. Local anesthesia can be combined with neuroleptanalgesia.

Toracoscopy can be performed under local anesthesia [25], but it should be carried out quickly in the cavity without adherence [25]. Cardiac and respiratory function should be monitored. The ideal candidate for local anesthesia is the cooperating and hemodynamically stable patient with no extensive intervention.

IV corticoid administration should be considered for the prevention of pulmonary edema (especially in major pleural effusions).

Locoregional (epidural) anesthesia is an effective alternative that can be used to continue postoperative analgesia. It can be associated with general anesthesia for optimal comfort for both surgeon and patient.

General anesthesia with simple tracheal intubation (low volume ventilated thoracoscopy) is only indicated in those cases where there is an abnormal pleural effusion with pulmonary collapse, or when there is a large, closed, thick-walled pleural collection (incarcerated) of lung. After drainage of collection, sometimes the lung expands, requiring "manual" ventilation to carry out the intervention in good condition.

General anesthesia with selective intubation is anesthesia of choice, being virtually indispensable for performing a quality thoracoscopic surgery [26]. Because minimally invasive techniques may have less time to undergo, can be administered short-acting intravenous drugs that augment inhaled anesthetics.

There are different double lumen endotracheal tubes: Robert-Shaw, Carlens, White [26, 27]. To verify correct positioning of probe, a flexible bronchoscope is required. Thus, the contralateral lung is ventilated, and the operated lung performs pulmonary collapse (after the parietal pleura incision), resulting a good quality collapse with a slower installation than the case of a thoracotomy.

Some authors supports pulmonary collapse by injecting CO_2 with a pressure up to 6–8 mmHg, and others believe that this collapse can only be achieved and maintained by insufflations without selective intubation. Excessive insuflation of carbon dioxide may generate intraoperative hypotension due to mediastinal displacement and reduced venous return to heart [28]. Insuflation is rarely recommended, except for patients with significant obstructive disease (under a pressure of less than 10 mmHg and a rate of 1.5 L/min).

Extubation of patient is often done on the operating table.

Concept of Cervical and Thoracic Border Surgery

Cervical and thoracic border is the anatomical-surgical region delimited (1) above by horizontal plane located at C6 vertebra and (2) inferior by the horizontal plane previously delimited by the sternal manubrium, and (3) posterior by the vertebral body T4 (Fig. 4) [29].

There are approximately 11 surgical specialties which have the cervical and thoracic border region in the theater of operations: thoracic surgery, general surgery, ENT surgery, cardiovascular surgery, neurosurgery, orthopedic surgery, plastic and reconstructive surgery, oral and maxillofacial surgery, endocrinological surgery, war surgery, and endoscopic surgery.

The most common diseases requiring cervical and thoracic cervical surgery can be listed according to the anatomical structures affected at this level:

Larynx

- Trauma
- Subglottic stenosis
- Subglottic cancer.

Trachea

- Wounds, tears
- Stenosis
- Tumors
- Tracheoesophageal fistula
- Tracheoarterial fistula.

Esophagus

- Pharyngeal-esophageal wounds
- Pharyngeal-esophageal functional disorders
- Zenker diverticulum
- Benign tumors
- Malignant tumors
- Caustic stenosis.

Thyroid

- Acute and chronic thyroiditis
- Thyroid abscess
- Cervical-mediastinal goiter
  - Thyroid cancer

Thymus

- Thymic hyperplasia
- Thymic cyst
- Thymic tumors
- Myasthenia gravis.

Parathyroids

- Hyperplasia
- Adenomas
- Carcinomas.

Great vessels

- Wounds and tears
- Stenosis
- Aneurysms.

Thoracic duct

- Fistula
- Thoracic duct cyst.

Pleural dome and cupula

- Apical pachypleuritis
- Apical pleural effusion
- Fibrous tumors
- Pulmonary Apical Cancer.

Superior thoracic aperture

- Manubrium tumors
- Tumors of ribs I-II
- Cervical rib
- Scalene myofascial pain syndrome
- Cancer of pulmonary apex with invasion of superior thoracic aperture (Pancoast-tumors).

Clavicle

- Fractures (trauma)
- Tumors
- Infections.

Cervical-thoracic spine

- Trauma
- Disc hernias

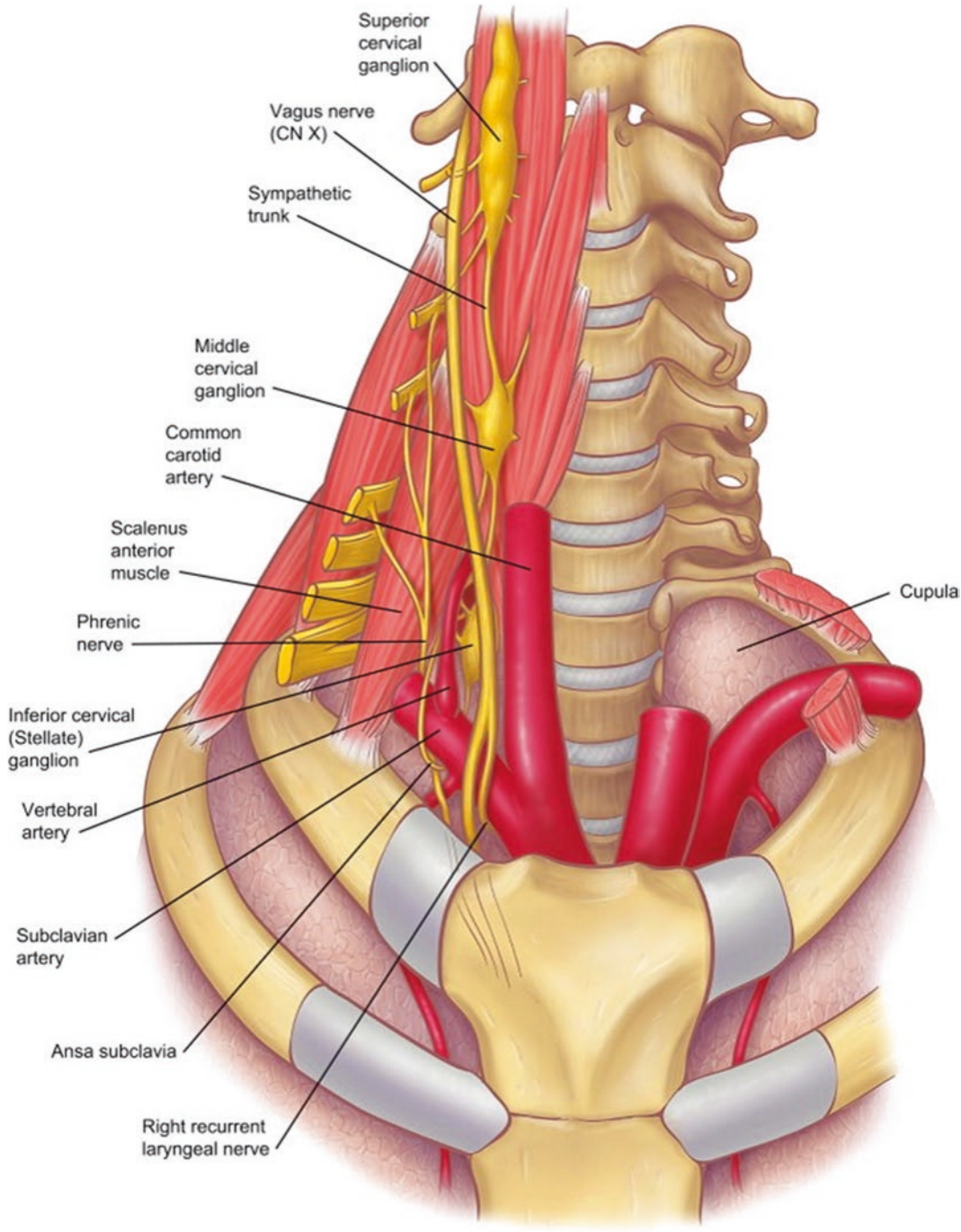


Fig. 4 Anatomy of the cervico-thoracic region. From [29] with permission

- Tumors
- Infections.

Peripheral nervous system
Neurogenic tumors of vagus nerve, phrenic nerve, sympathetic trunk, brachial plexus, intercostal nerves II–III.

Lymphatic nodes

- Lymphadenitis (nonspecific/specific)
- Primary tumors (lymphomas) and secondary (metastases).

Small vessels

- Cervico-mediastinal hemangiomas
- Cervico-mediastinal limphangiomas (hygroma cystica).

Adipose tissue
- Cervico-mediastinal lipomas.

Connective tissue
- Tumors

– Benign (fibromas)
– Malignant (sarcoma).

Others

- Pneumomediastinum
- Mediastinal hematoma
- Cervical mediastinitis
- Cervical and mediastinal fibrosis

Surgical Approaches of Cervico-Thoracic Junction Pathology

1. **Classic surgical approaches of the cervico-thoracic junction pathology**

Cervicotomies

Lateral Cervicotomy
It is accomplished along anterior border of the sternocleidomastoid muscle, providing an adequate exposure both for diagnostic surgical procedures (lymphatic node or cervico-thoracic tumor biopsy) and for curative ones (cervical lymphadenectomy, pharyngo-esophageal diverticulectomy or esophageal reconstruction after esophagectomy, congenital cervicothoracic disorders).

Technical steps:

1. Diverticulectomy using linear stapler with one layer manual suture for safety;
2. Left common carotid artery retracted laterally;
3. Left lobe of the thyroid gland;
4. Pharynx.

Suprasternal Cervicotomy
Cervical incision is effectuated in a transversal manner (cervicotomy type Kocher) (Fig. 5) in most of cases [30]. It represents a good approach of the cervico-thoracic region for both diagnostic (lymphatic or cervico-thoracic tumor biopsy) and curative surgical procedures (removal of the cervico-thoracic goiter with inferior pole situated up to the aortic arch, repair of post intubation lesions of the cervico-thoracic part of trachea, radical cervical lymphadenectomy, or adequate drainage in descending cervicomediastinitis).

Some situations require a large transversal cervicotomy or an "**Y-shaped**" cervicotomy (for extirpation of a big cervico-thoracic goiter or for a radical cervical lymphadenectomy and neck dissection in the head and neck cancers) (Fig. 6) [31].

Supraclavicular Cervicotomy (Fig. 7a–d) [32]
Supraclavicular approach of cervico-thoracic border pathology is used for arterial lesions requiring control of proximal subclavian artery, for resection of aneurysm or stenosis and bypass graft placement as for resection of the cervical rib (when is present) or of first rib in the thoracic outlet syndrome. The supraclavicular approach for the excision of first rib relieves thoracic outlet syndrome by decompression of the brachial plexus in the interscalene region. The lower nerve trunk and C8 and T1 nerve roots must be

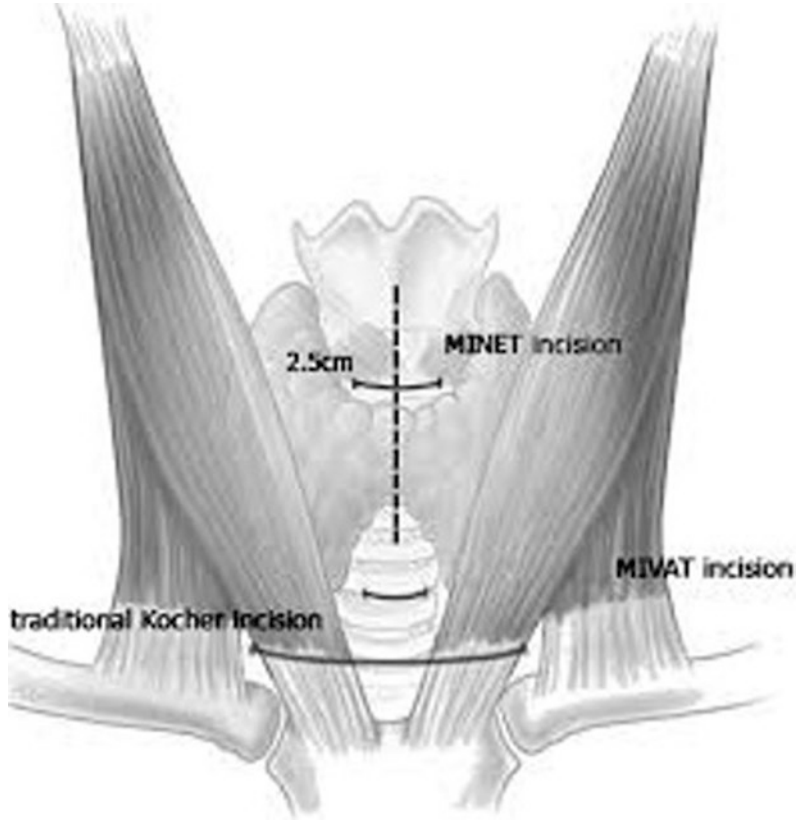


Fig. 5 Kocherincision. From [30] with permission

protected as the most posterior aspect of first rib is resected under direct vision. Also, any cervical ribs or prolonged transverse processes are easily removed by this supraclavicular approach.

2. **Anterior cervico-thoracic incisions (anterior transcervical approaches)**

Transclavicular (Fig. 8a–g) [33, 34]
Performing of ***L-shaped incision cervicotomy*** includes a vertical presternocleidomastoidal incision prolonged horizontally below the clavicle up to the deltopectoral groove. However, to increase the exposure and make the entire resection through this incision only, interception between the vertical and horizontal branches of the L-shaped incision is lowered at the level of the second or third intercostal space (Fig. 8a) [33, 35].

After performing division of sternal and clavicular attachment of the sternocleidomastoid muscle along with the upper digitations of ipsilateral pectoralis major muscle from the clavicle, a myocutaneous flap is folding back to give a full exposure of neck with thoracic inlet and upper part of the anterolateral chest wall [33]. The scalene fat pad is pathologically examined (cervical lymph node micrometastases) after divided inferior belly of the omohyoid muscle. The ipsilateral superior mediastinum is inspected by operator's finger along the tracheoesophageal groove, after division of the sternothyroid and sternohyoid muscles. The tumor's extension to the thoracic inlet is then carefully assessed. We perform resection of the internal half of the clavicle only if the tumor is considered resectable [33].

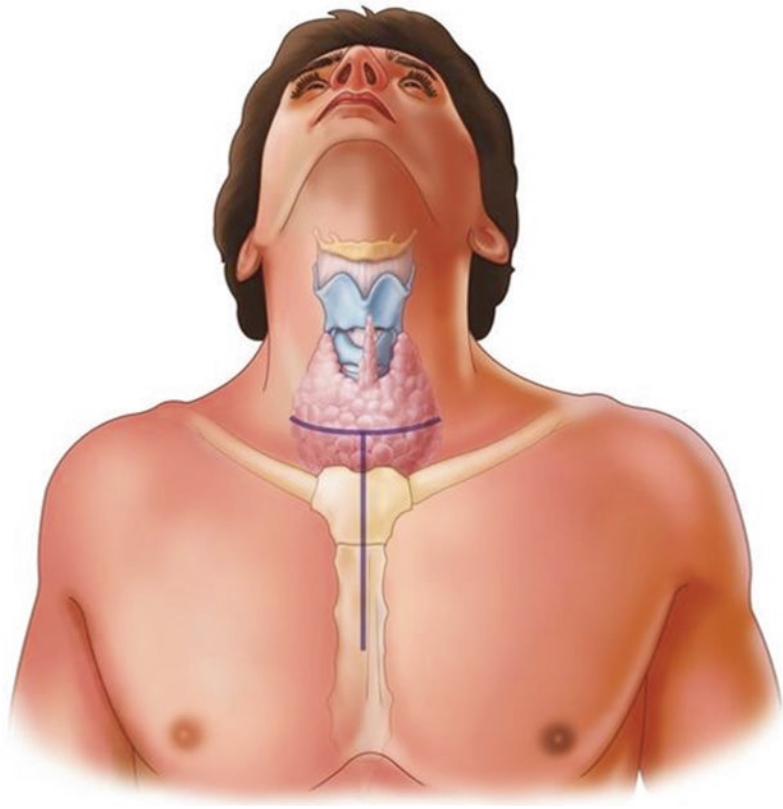


Fig. 6 "**Y-shaped**" cervicotomy. From [31] with permission

Through this approach we can perform: chest wall resection after division of the anterior and middle scalene muscles (the anterolateral arch of first rib is divided at the costochondral junction and then disarticulated from the transverse process of T1, the second rib is divided at the level of its middle arch then disarticulated from the transverse process of T2 and the third rib is scraped on the superior border toward the costovertebral angle), dissection of the brachial plexus (nerve roots of C8 and T1 are then easily identified and dissected until their confluence forms the lower trunk of brachial plexus) with stellate ganglia removing from anterior surface of vertebral bodies of C7 and T1, dissection of subclavian vessels (do not hesitate to suture-ligate the internal jugular vein, the subclavian vein or the innominate vein if the tumor venous extension is present and subclavian artery is then dissected and freed following a subadventitial plane or the artery is divided and revascularization is performed either with PTFE graft (6 or 8 mm) or, more often, with an end-to-end anastomosis). On the left side, ligation of the thoracic duct is usually required [33].

The pleural space is usually opened by dividing Sibson's fascia. Through this cavity an upper lobectomy can be performed to complete the operation. The upper lobectomy and the chest wall resection of first four ribs can be performed through the transcervical approach only without recurring to the posterolateral thoracotomy [33].

If apical tumor is involving intervertebral foramen and part of the ipsilateral vertebral body, the tumor is usually first approached anteriorly and then surgery is completed through a hemivertebrectomy performed through a posterior cervical midline approach [33].

There is increasing concern regarding the aesthetic and functional discomfort of the

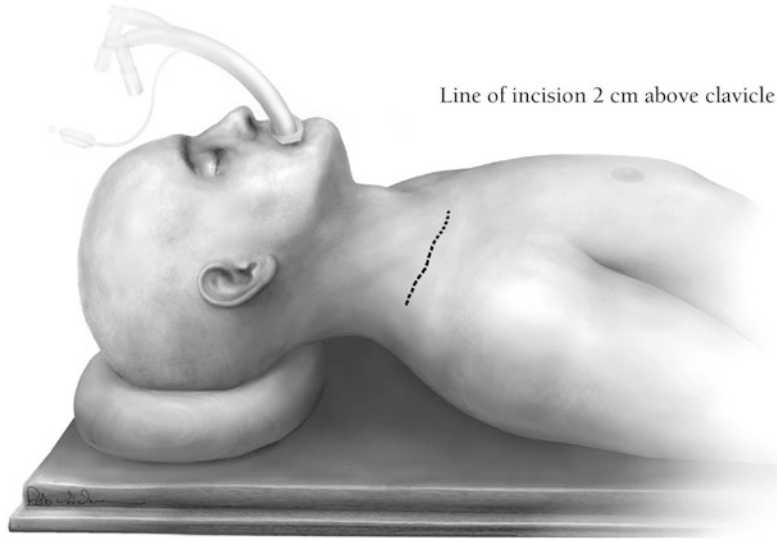
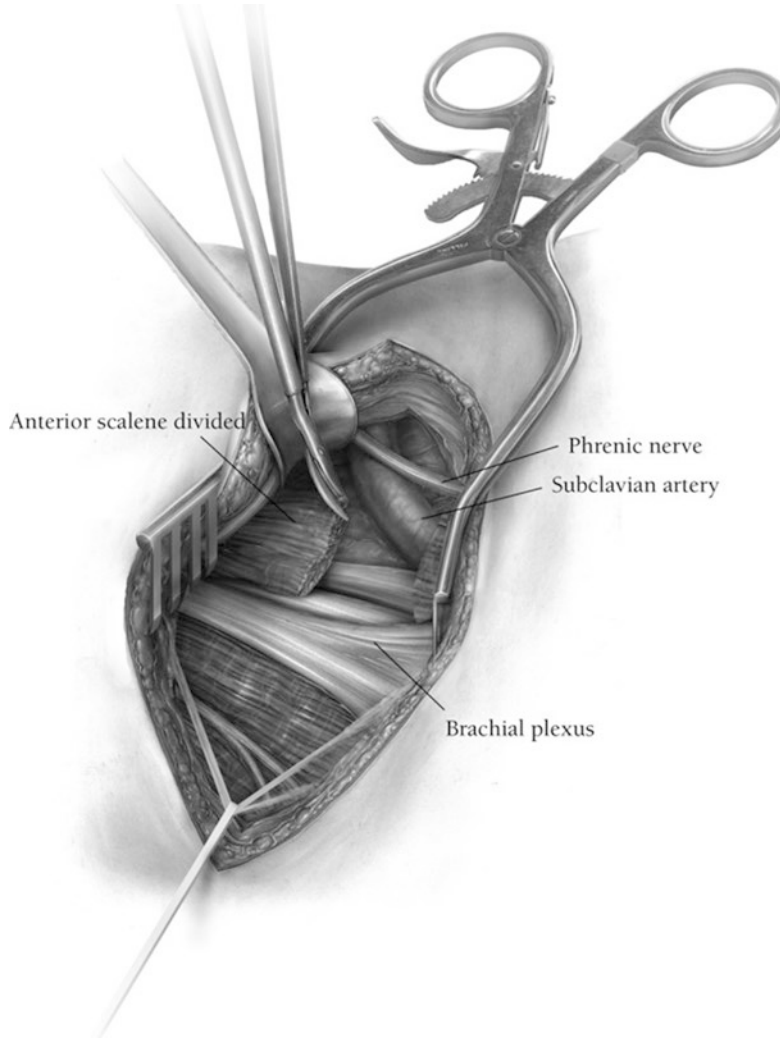


Fig. 7 **a** An incision is made in the supraclavicular fossa, in a neck crease parallel to and 2 cm above the clavicle. From [32] **with permission**. **b** The anterior scalene muscle is divided from the first rib, and the subclavian artery is noted immediately behind this. An umbilical tape is placed around the subclavian artery. The phrenic nerve is not mobilized, but rather is protected by direct visualization, while the anterior scalene muscle is divided. From [32] with permission. **c** The upper, middle, and lower trunks of the brachial plexus are easily visualized and gently mobilized. The middle scalene muscle is now divided from the first rib. It has a broad attachment to the first rib, and care must be taken to avoid injury to the long thoracic nerve, which in this position may have multiple branches and may pass through or posterior to the middle scalene muscle. From [32] **with permission**. **d Rongeur technique** facilitates removal of the entire posterior portion of the rib (with the nerve roots reflected anteriorly), preventing new bone formation and the potential for production of recurrent compression From [32] with permission

anterior transclavicular approach (the resection of internal half of clavicle, pushes the shoulder anteriorly and medially, especially in combination of resection of long thoracic nerve with scapula alata presence). If this is anticipated is better to perform an oblique section of manubrium with fully preservation of sternoclavicular articulation, rather than the simple sternoclavicular disarticulation [33].

Transmanubrial [36]

The skin incision is performed through an ***L-shaped cervicotomy*** (Fig. 8a) with the upper line on anterior part of sternomastoid muscle down to the angle of manubrium and two fingers below the clavicle. The sternomastoid muscle is dissected along its anterior part from cervical tissue up to internal jugular vein, major pectoral muscle is spared, and sternal manubrium is exposed. Internal thoracic artery is divided. Upper part of manubrium is sectioned through *L-shaped incision*, respecting the sternoclavicular articulation. First costal cartilage is resected. This permits mobilization of an osteomuscular flap that is progressively elevated following the posterior part of clavicle and give dissection with vascular safely control, leaving the subclavian muscle on subclavian vessels. Afterward, starting from the internal jugular vein and Pirogoff confluence, the subclavian vein is carefully dissected from the subclavian muscle. Mobilize the main venous axis and expose phrenic nerve and anterior scalene muscle. The subclavian artery is then carefully dissected, and brachial plexus and posterior part of first rib are eliberated. At the same time, carotid common arteries can be controlled. The partial manubrial resection and first rib resection permit control of the superior vena cava and main aortic branches. This approach gives excellent access



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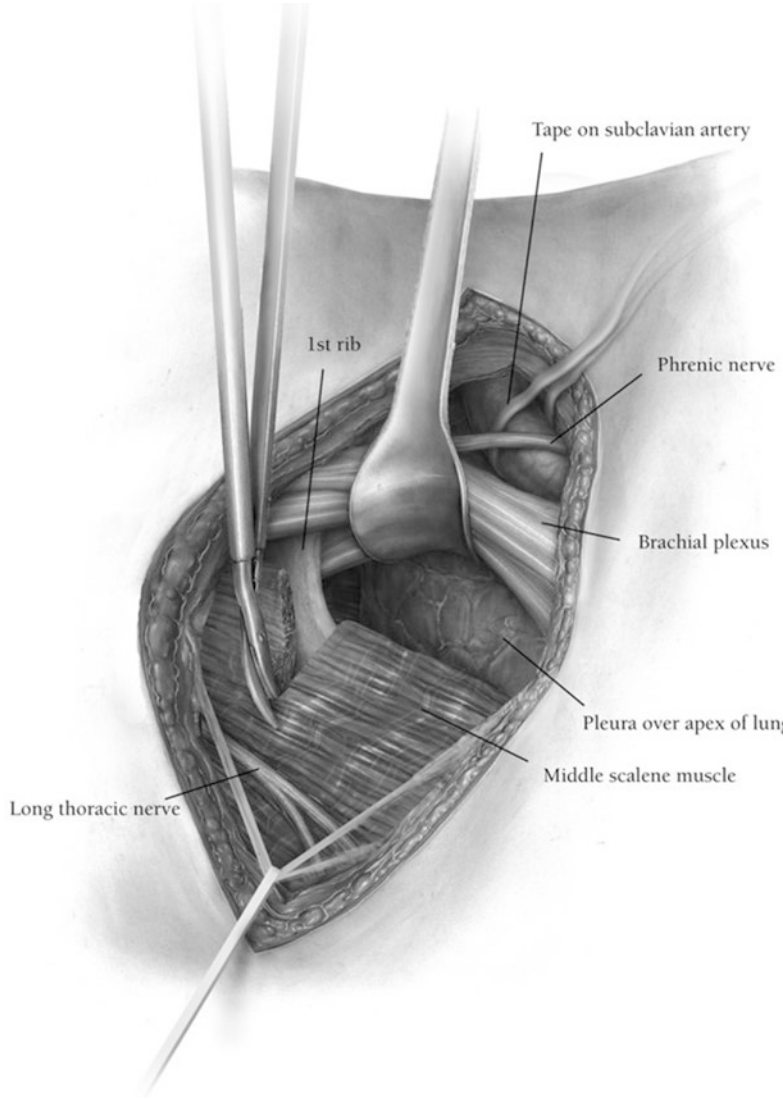
to the anterior part of vertebral bodies (from C3 to T3). Manubrium osteosynthesis is performed by means of two separate steel threads.

Transmanubrial approach provides same surgical advantages as anterior transclavicular approach, avoiding its functional and aesthetic disadvantages of anterior approach for apical chest tumors. Transmanubrial approach give an excellent exposure of the apex of lung, and safe control and resection of thoracic outlet structures. It spares in situ the clavicle without muscular sacrifice. It maintains full shoulder girdle movement and important early and long-term postural advantages associated with excellent aesthetic results.

The superior sulcus lesion extending to the thoracic inlet may be resected by the anterior transcervical approach [37]. Non-small cell lung carcinoma represents the most frequent cause of superior sulcus lesions (Pancoast tumors). These anterior cervico-thoracic incisions are used for approaching the Pancoast tumors located in front of the anterior scalenus muscle. These tumors may invade the platysma and sternocleidomastoid muscles, first intercostal



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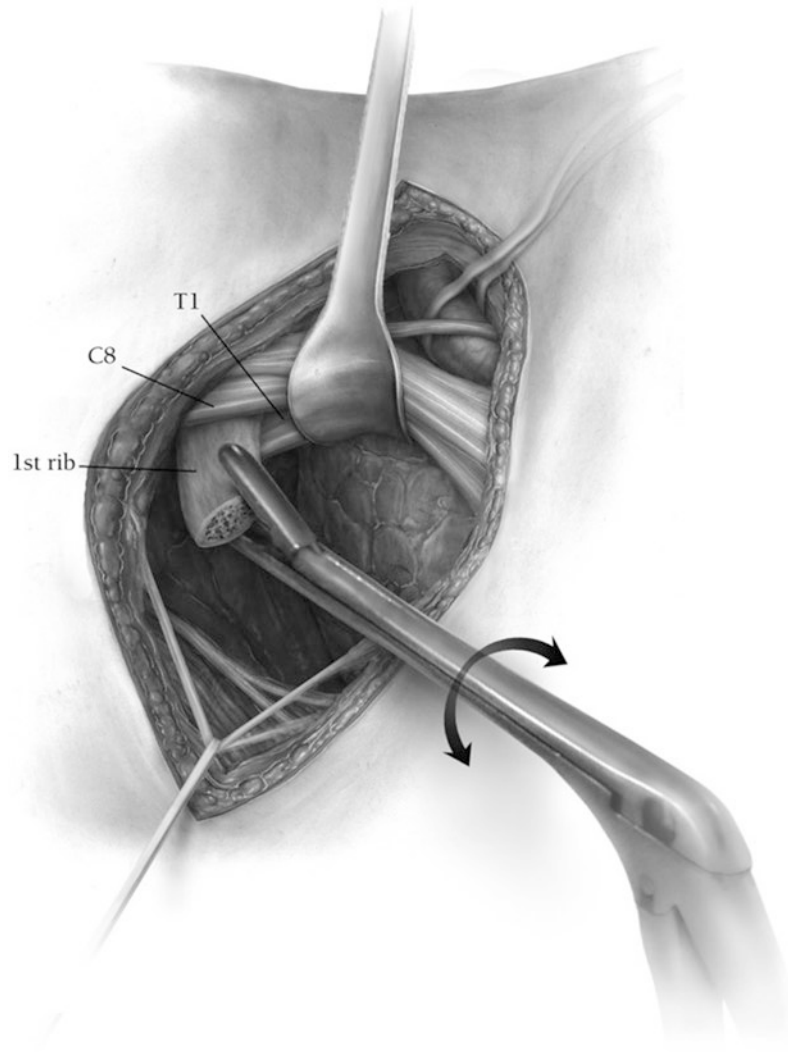
nerve and first ribs, external and anterior jugular veins, subclavian and internal jugular veins and their major branches, and scalene fat pad. The cervico-thoracic anterior approach is also being accepted as standard for all benign and malignant lesions of the thoracic inlet structures other than bronchogenic cancers as well, e.g., osteosarcomas of the first rib, tumors of the brachial plexus [38]. In cases of non-small cell lung carcinomas with upper thoracic inlet invasion (Pancoast tumors), the goal of surgery is resection of upper lobe of the lung along with invaded cervico-thoracic structures. This scope can be reached by an anterior transcervical approach possibly followed by the thoracic approach for pulmonary resection (classically



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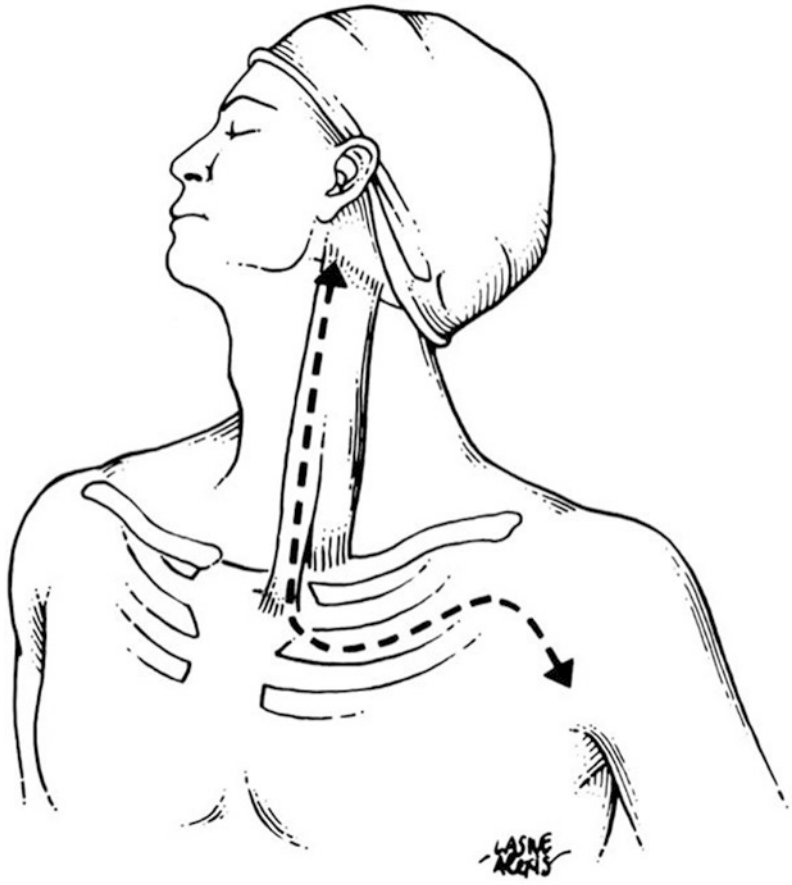
approaches like Shaw-Paulson or axillary thoracotomies or VATS lobectomy).

3. **Anterior cervico-sterno- thoracic incisions**

Hemiclamshell or Trapdoor Incision (Fig. 9a, b) [39]

The ***hemiclamshell incision*** consists of an antero-lateral thoracotomy usually in the fourth or fifth intercostal space, associated with a partial longitudinal median sternotomy. The hemiclamshell incision can be diverted into a "trapdoor" incision or "book thoracotomy" [39] by extending the upper border of median sternotomy towards neck with an incision along the anterior edge of sternocleidomastoid muscle.

Tumors involving the cervico-thoracic junction with extension to one chest cavity or in the anterior mediastinum are usually difficult to access by VATS tehniques or by classical incisions such as a postero-lateral thoracotomy or median sternotomy. Alternative incisions such as anterior cervico-thoracic approaches



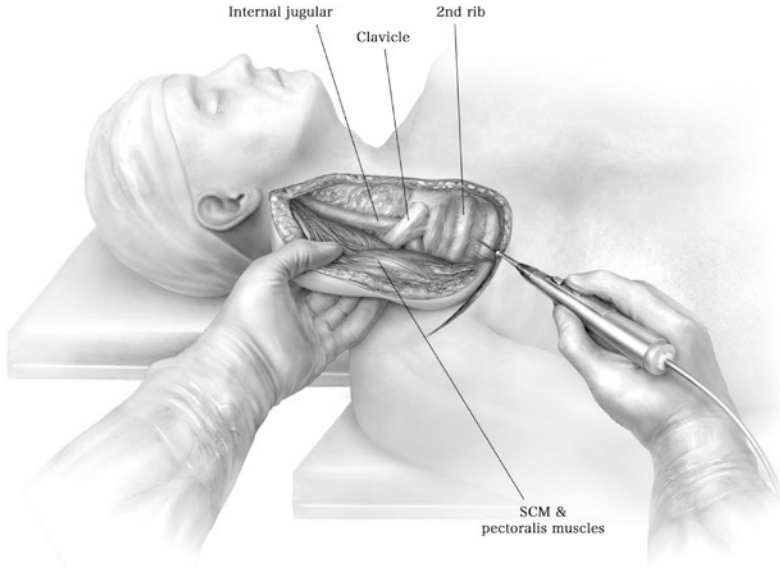
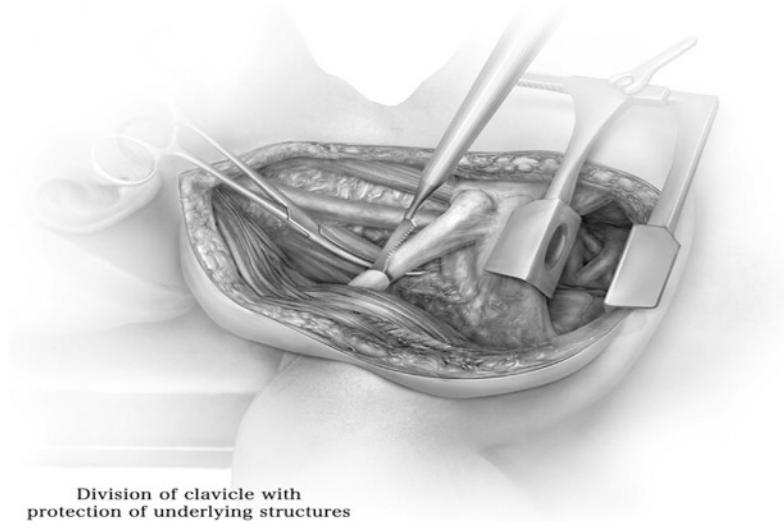

Internal jugular
Clavicle
2nd rib
SCM &
pectoralis muscles

Fig. 8 **a** Left *L-shaped* cervicotomy. Skin incision is made from angle of mandible down to sternal notch after anterior border of sternocleidomastoid muscle and is extended horizontally under internal half of the clavicle as far as deltopectoral groove. From [35] With permission. **b** The incision is deepened with cautery down to the chest wall. The sternocleidomastoid (SCM) and pectoralis major muscles are dissected off the manubrium, clavicle, and chest wall. The sternal attachment of the SCM is divided sharply so it can be reattached on the manubrium at the end of the surgery. The muscles attachments are cauterized off the clavicle so the proximal one third of the clavicle is exposed. The muscle and the skin are folded laterally together as a myocutaneous flap. The preservation of a myocutaneous flap is important to obtain adequate healing of the wound as patients with lung cancer invading the thoracic inlet often undergo induction chemoradiation therapy before surgery. This provides exposure to the strap muscles, internal jugular vein, scalene fat pad, and anterolateral chest wall. From [34] **with permission**. **c** Resection of the internal half of the clavicle only if the tumor is considered resectable (by disarticulating the claviculosternal joint and by sectioning the proximal one third of the clavicle with the saw) From [34] with permission. **d** The anterior scalene muscle is sectioned above the tumor, preserving the phrenic nerve if necessary. The subclavian artery can be exposed and controlled proximally and distally to the tumor. Its branches are ligated and sectioned to facilitate exposure. The vertebral artery can be resected if necessary. The subclavian artery can be clamped and sectioned on each side of the tumor if it is invaded. A bolus of heparin (50 units/kg) is given before clamping the subclavian artery. The vagus nerve should be localized and preserved when dissecting the internal jugular vein on the right or the left side. On the right side, the recurrent nerve should also be localized and preserved as it loops around the subclavian artery. Damage to the right recurrent nerve should be avoided when the proximal part of the subclavian artery is clamped. The first and second ribs remain attached to the tumoral specimen with the lower portion of the anterior scalene muscle and are resected en bloc with the tumor. The first and second ribs were removed from this drawing and some of the subsequent drawings to demonstrate the anatomy more clearly. n = nerve. From [34] **with permission**. **e** The right upper lobectomy can be performed through the second intercostal space. The lobectomy is performed from an anterior to a posterior approach. The right upper lobe pulmonary vein and artery are ligated or stapled and the fissure is completed with staplers. The bronchus is then stapled. The right upper lobe can then be removed en bloc with the tumor. A lymph node dissection of stations 2R and 4R on the right side and stations 5 and 6 on the left side is then performed through the anterior approach as part of the oncologic procedure. Station 7 is also sampled or dissected according to the exposure. From [34] with permission. **f** The head of the first and second ribs can be disarticulated from the vertebra if the costotransverse foramen, the neural foramen, and the vertebral body are not involved. If the costotransverse foramen is involved, the anterior part of the vertebral body can be exposed and sectioned with a chisel to remove the lateral edge of the vertebral body and the transverse process at the level of T1 as shown on the figure. If the neural foramen and/or the vertebral body are involved, a hemivertebrectomy or a total vertebrectomy of T1 is required. In these cases, a posterior midline approach must be associated with the anterior approach to perform the laminectomy, ligation of nerve roots in the spinal canal, and posterior vertebral body osteotomy. If a hemivertebrectomy is performed, a posterior spinal stabilization is required. If a complete vertebrectomy is performed, a posterior and an anterior spinal stabilization are required. The posterior spinal stabilization can be performed from the posterior midline approach. The anterior transclavicular approach, however, does provide adequate exposure to instrument at the anterior part of the spine if further stabilization is required. From [34] with permission. **g** The subclavian artery is reconstructed with an interpositional graft such as polytetrafluoroethylene ringed graft 6 to 8 mm. From [34] with permission



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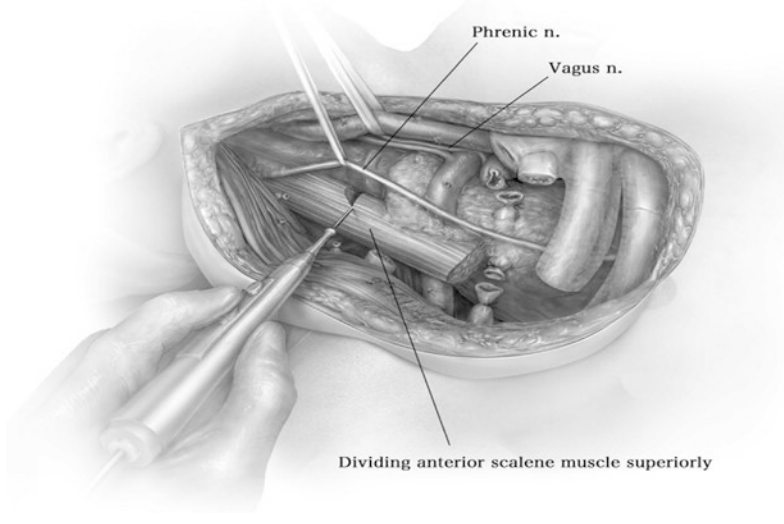

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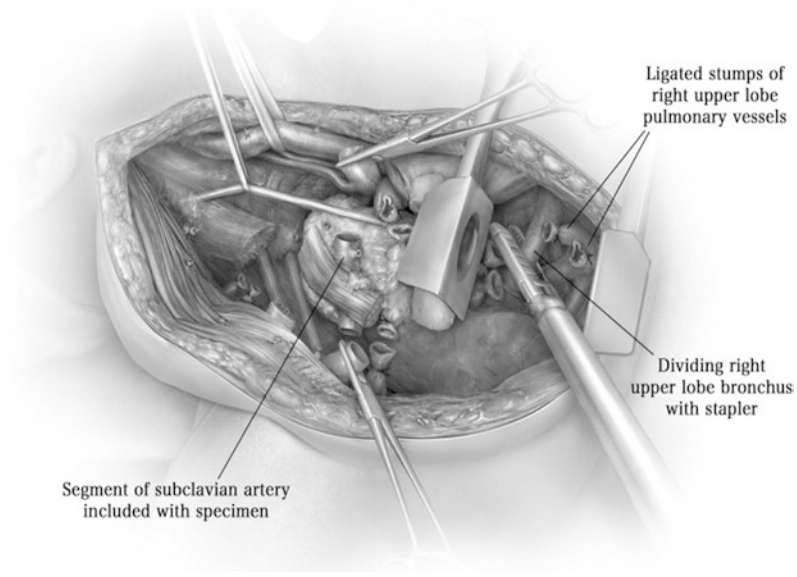

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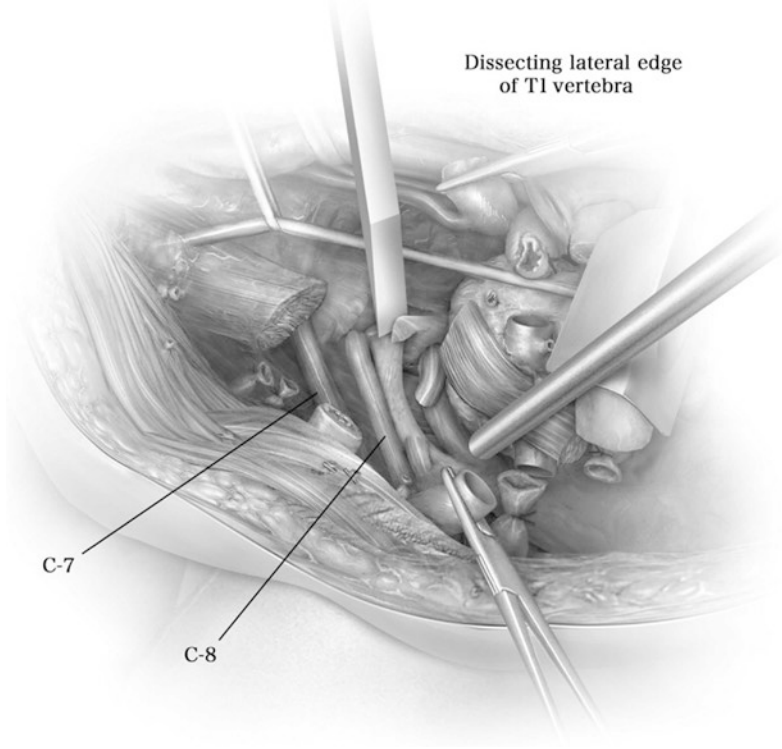

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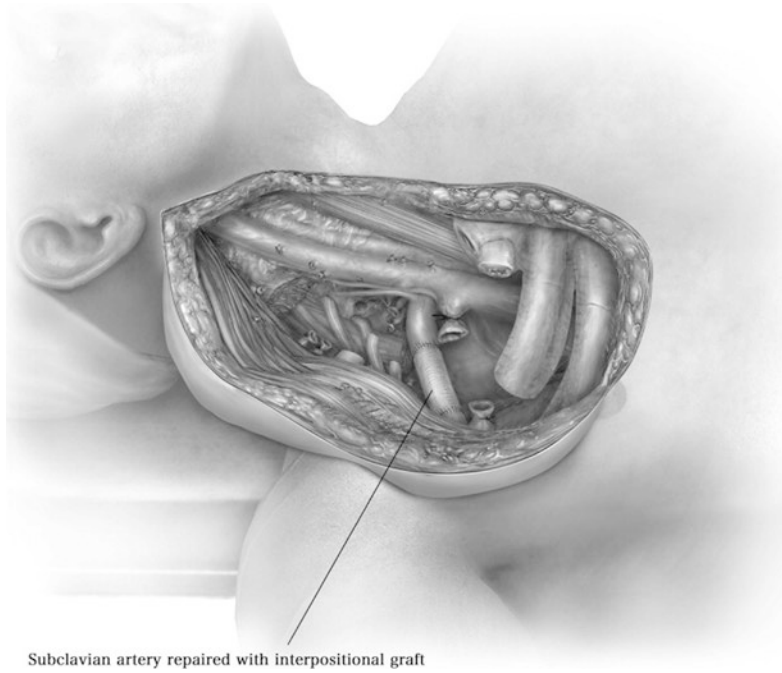

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(transclavicular or transmanubrial) may cause impaired shoulder girdle function, irritation of brachial plexus and cosmetic problems, especially if an additional thoracotomy is required. Hemiclamshell approach is a possible alternative in patients suffering from anterior cervico-thoracic tumor s or injuries to the subclavian vessels. First rib may be transsected laterally to the internal mammary vessels after identification and preservation of the subclavian vein, for a better access to the anterior cervicothoracic junction. The division of first rib will further improve exposure of anterior cervicothoracic junction with preservation of the shoulder girdle's integrity [40].

The hemiclamshell (trapdoor) incision provides a good access to injured subclavian arteries [40]. This incision is well suited for emergency situations because it can be performed with patient in supine position with a less manipulation of heart and a good access of the left chest cavity as compared to sternotomy [41].

In situation of Pancoast tumor invading anterior part of upper thoracic inlet, the superior vena cava and ipsilateral innominate vein are dissected and subclavian vein is found. After the assessment of resectability, the involved ribs are divided and the appropriate intercostal space below the visible tumor is accessed. The dissection and management of subclavian vein and artery and brachial plexus are made as outlined by the transclavicular approach. If it is necessary, the clavicle can be removed for better exposure of the subclavian vessels and brachial plexus [33].

Trans-sternal Incision

In 1979 Masaoka and colleagues described and anterior approach for managing the superior sulcus tumors invading the thoracic inlet involving the vascular compartment [44]. This includes a proximal median sternotomy, an incision in the anterior fourth intercostal space (below) and a transverse cervical incision at the base of the neck (above). The management of this region is

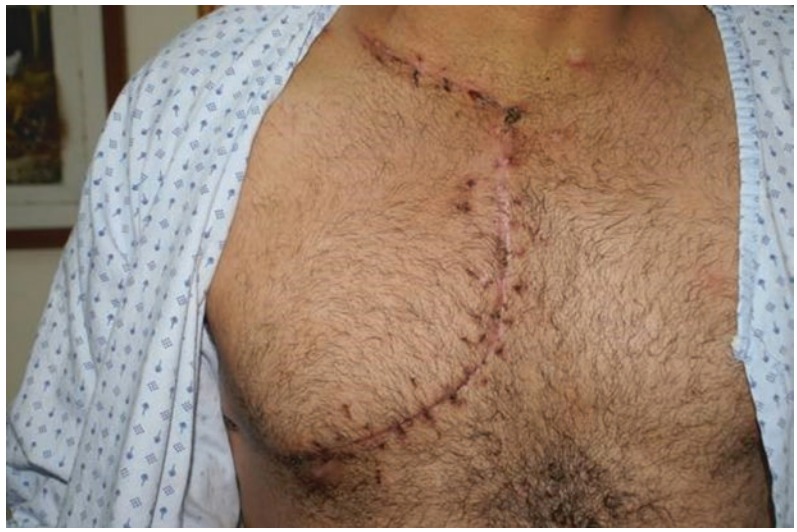
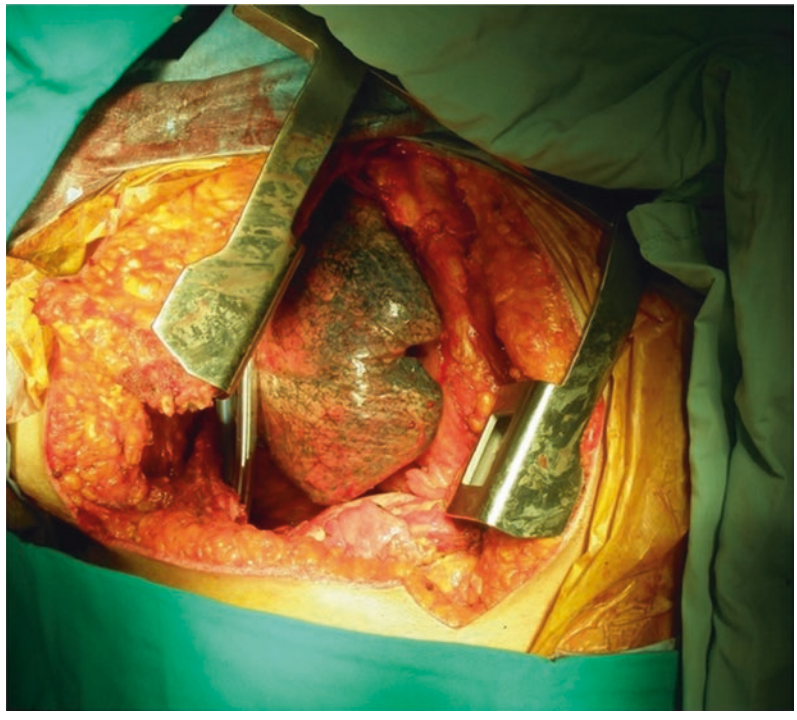


Fig. 9 **a** Displays how the incision was extended by a right anterolateral thoracotomy, performed through the third intercostal space. From [42]. **b** Hemiclamshell incision can be observed after removal of the tumor. A separator was placed on borders of the sternotomy incision. From [43]



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thereafter made as in the previously described approaches [44].

After division of the muscles of neck (sternocleidomastoid, sternohyoid and sternothyroid) the chest wall is retracted and access to vascular and nervous structures of the inlet is accomplished. After resection of chest wall and lung tissue the sternum is re-approximated and the divided muscles of neck and thorax are sutured. Disadvantages of this incision is mainly possible sternal dehiscence with flail chest.

Later, in 1993 the Masaoka group proposed a variation of their initial incision the so-called "hook approach" [45]. The anterior approach was suited for lesions in the anterior portion or middle portion and the *hook approach* for lesions in the middle or posterior portion.

Classification of anterior surgical approaches clasification

Trans-sternal [44]
Trans-clavicular [46]
Trans-scapular [37]
Hemiclamshell "trap-door" [39]
Transmanubrial (TMA) [36]

Combined Anterior Surgical Approach for Pancoast tumors [36]:

TRANSMANUBRIAL Alone
TRANSMANUBRIAL + Thoracotomy lateral/posterior
TRANSMANUBRIAL + VATS
TRANSMANUBRIAL + HEMICLAMSHELL
HEMICLAMSHELL Alone

Characteristics of the various anterior approaches are presented by Table 1 [36]:

4. **Thoracotomies** (for cervico-thoracic region approaches)

Postero-lateral
Trans-scapular (the antero-posterior hook approach)
Axillary.

Postero-Lateral Thoracotomy [47]

Is indicated mostly in cases of non small cell lung carcinomas of lung with posterior invasion of structures from upper thoracic inlet (Pancoast lung tumors with posterior invasion). These tumors are usually located in costovertebral groove and are situated posterior to the middle scalenus muscles and usually invade the nerve roots of T1, posterior part of subclavian and vertebral arteries, paravertebral sympathetic chain, inferior cervical (stellate) ganglion and prevertebral muscles.

A long posterior thoracotomy incision is made [47]. It describes an arch that starts superiorly between spinous process C7 of the seventh cervical vertebra and the medial part of scapula, extends downward 2 cm below the inferior angle of scapula, and ends 2 cm beyond it or just lateral to the breast in women. The incision is then carried deeper with electrocautery through muscles like latissimus dorsi, serratus anterior, trapezius, levator scapulae and rhomboideus minor and major, avoid injury of dorsal scapular nerve

Table 1 *Characteristics of the various anterior approaches*

Approach	Advantages	Disadvantages
Trans-cervical	Excellent exposure All type of lung resection Feasible without accessory thoracotomy	Resection of the clavicle Risk of scapula alata
Trans-manubrial	Excellent exposure Leaves in situ the clavicle without muscular sacrifice	Needs an accessory thoracotomy or resection of the first two ribs to perform the lung resection
Hemiclamshell	Excellent exposure	Difficult posterior dissection Risk of fail chest
Trans-scapular	Adequate exposure	Very long ischemic incision Increased shoulder girdle dysfunction of impairment of pulmonary function

and satellite scapular artery (which run down on medial border of scapula). Scapula, fully mobilized from chest wall, is then retracted upward and forward. After the assessment of tumor resectability (evaluation of the tumor's extension on thoracic chest wall, thoracic inlet, lung and mediastinum), the thorax is then accessed through intercostal space below the lowest rib to be resected, as determined by preoperative CT scan or MRI (usually the third intercostal space). For local resection to be complete, one intact rib with its intercostal muscles below the lower margin of lesion is removed. The chest wall resection should be made first, that it can then be released into the pleural cavity allowing a safer pulmonary resection [47].

Through this approach we can perform: *chest wall resection*, *dissection of the brachial plexus* (the lower trunk of the brachial plexus with the roots of the eighth cervical nerve and first thoracic nerve situated above and below the neck of first rib), *dissection of subclavian vessels* (subclavian artery resection and reconstruction and resection and simply ligation of subclavian vein – in a situation of tumor vascular invasion), *upper thoracic vertebral body resection* (up to one-quarter of vertebral body may be resected without affecting stability) with stellate ganglia removing. Since the management of the subclavian vessels is very demanding through the posterior approach (tumoral invasion is present beyond the subclavian vessels), an option should be to continue the surgery through additional anterior approach [33].

The main disadvantage of standard postero-lateral thoracotomy is the poor exposure of anterior cervico-thoracic junction. The visualization and access to anterior mediastinum is limited, and lateral position required for thoracotomy may not be tolerated in emergency situations (hemodynamically unstable patients) [40].

Trans-scapular Thoracotomy (The Antero-posterior Hook Approach)

The classic anterior-posterior hook approach was described in 1993 by Masaoka group and colleagues from Nagoya. This approach involves a classic posterolateral thoracotomy that is curving upward anteriorly toward the sternoclavicular joint [45].

The hook approach is selected for superior sulcus tumors and anterior apical tumors without involvement of sternum. A long curved periscapular skin incision around the axilla from the level of seventh cervical vertebra to the midclavicular line above the nipple is performed. Changing the position of patient by tilting the operating table and moving the arm offers safe and complete exposure of the entire thoracic inlet. Resection of subclavian vessels followed by reconstruction with a graft and dissection of brachial plexus are easily performed. Furthermore, the ipsilateral supraclavicular lymph nodes can be resected through same incision.

Structures as vertebrae, brachial plexus, subclavian vessels and ipsilateral supraclavicular lymph nodes could be resected by the hook approach (for lesions in the middle or posterior compartment of the upper thoracic inlet).

However, the "hook approach" did not obtain great popularity because of the enormous extension of incision, leading to serious wound closure complications.

Axilary Thoracotomy (for Thoracic Outlet Syndrome) (Fig. 10)

Thoracic outlet syndrome refers to compression of subclavian vessels and brachial plexus at the superior aperture of chest. Various syndromes are similar (scalenus anticus, costoclavicular, hyperabduction, cervical rib, and first thoracic rib syndromes), and the compression mechanism

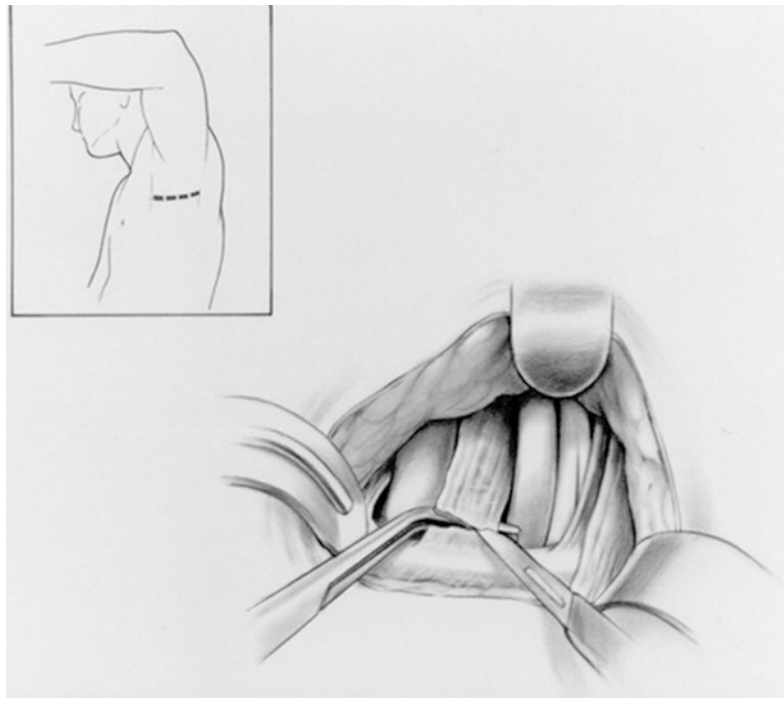

Fig. 10 The incision for the transaxillary resection is made transversely below the axillary hairline between the pectoralis major and latissimus dorsi muscles. The incision is carried directly to the chest wall without angling up toward the first rib. When the chest wall is encountered, the dissection is directed superiorly to the first rib, identifying the intercostal brachial nerve as it exits between the first and second ribs. The nerve is preserved by retracting it anteriorly or posteriorly. (Division of this nerve produces up to 6 months of paresthesias on the inner service of the upper arm, which may be very disturbing to the patient). If adhesions are present, it is necessary to perform a careful lysis of these. In this instance the neurovascular structures are dissected carefully off the chest wall in order to visualize the first rib. The first rib is dissected subperiostally with a Shaw-Paulson periosteal elevator and the scalenus anticus muscle identified. The right-angle clamp is placed behind the muscle, being careful not to injure the subclavian artery or vein. The scalenus anticus muscle is divided near its insertion on the first rib. (This procedure avoids injury to the phrenic nerve, which courses from laterally to medially across the anterior surface of the muscle.) From [48] with permission

is often difficult to identify. Most compressive factors operate against the first rib.

The transaxillary approach of first rib is reserved for intermittent or total axillary-subclavian venous occlusion (Paget-Schroetter Syndrome), for neurological compression or combinations of these [48].

5. Cervicosternotomies

Partial Cervicosternotomy with Transversal Cervical Incision

It offers adequate exposure of cervico-thoracic goiter (majority with the inferior pole situated below the aortic arch) with very good approach of inferior thyroid artery and vein and very good approaches of the lesions of cervico-thoracic part of trachea.

Partial Cervicosternotomy with Unilateral Vertical Cervical Incision

Cervical incision is made along medial border of right or left sternocleidomastoid muscle and extended down to suprasternal notch. Then thoracic part of incision extends into the anterior sternal midline to the level between second and third ribs for partial upper sternotomy.

This incision shows adequate exposure of anterior cervico-thoracic spine for C6–T3

vertebral pathology: infection (TBC, pyogenic, parasites), malignancy (metastatic, primary tumor, adjacent invasion), degenerative (herniated nucleus pulposus), trauma (fracture-dislocation, compression fracture), spinal deformities (scoliosis, kyphosis, lordosis). T3 is caudal limit of exposure (determined by the brachiocephalic vessels) and we must avoid lesion of the innominate artery by high-speed drill (use a long-bladed retractors).

The right side cervical approach presents both advantages (avoid the thoracic duct lesion) and disadvantages (risk of right recurrent laryngeal nerve lesion) and must take some precautions like carefull ligation and section of inferior thyroid artery and vein and gently traction with mobilization of trachea and esophagus for an adequate exposure of the cervico-thoracic spine.

6. **Combined Approaches**:

Cervicotomy and thoracotomy
Cervicosternotomy and toracotomy
Cervicotomy and sterno-toracotomy.

These approaches are useful as diagnostic and curative surgical procedures in a large area of cervico-thoracic junction pathology: cervico-thoracic thyroid gland pathology, infection disorders (cervico-mediastinitis), secondary or primary tumors of the cervico-thoracic anatomic structures, and traumatic injuries of vertebral spine or organs situated in the cervico-thoracic region (like postintubation tracheal lessions).

Minimally Invasive Approaches of the Cervico-Thoracic Junction Pathology

Cervical mediastinoscopy
Anterior mediastinoscopy
Thoracoscopy
Combined mediastinoscopy and thoracoscopy.

These minimally invasive approaches of the cervico-thoracic region are accurate as diagnostic and staging surgical procedures in the evaluation of cervico-mediastinal limph node metastasis in lung cancer, cervico-mediastinal tumors, cervico-mediastinal extension of lung tumors.

In the modified tehniques these approaches are very useful in some curative surgical procedures like VAMLA and TEMLA (for cervical and mediastinal limphadenectomy in lung cancer) and minimally invasive thymectomy for myastenia gravis for complete removal of the whole thymus and all ectopic thymic foci dispersed in the fatty tissue from various areas in the neck and mediastinum: Complete Thoracoscopic Thymectomy (cT-Thymectomy), Robotic Thymectomy, Transcervical-Subxiphoid-VATS Maximal Thymectomy.

Therefore VATS offers an excellent visualization of anatomical structures of thoracic inlet and has been introduced in the diagnosis and treatment of Pancoast tumors. It allows observation of chest wall invasion to help surgeon to confirm or change the surgical strategy intraoperatively [49].

VATS is an useful diagnostic tool to examine the extent of tumor to thoracic chest wall, thoracic inlet, lung, mediastinum, and level of subclavian vessels involvement. Roviaro et al. suggested routine use of VATS as intraoperative staging for lung cancer and for resectability of lesion [50]. Later, Vallieres et al. reported the use of thoracoscopy for staging and assessment of resectability only for Pancoast tumors [51]. Koshiko et al. announced a case of an en bloc resection of a Pancoast tumor using VATS. Their patient was treated with an anterior transcervical approach and assisted by thoracoscopy in supine position, which was then converted to a posterior thoracotomy to complete surgery without video-assistance [52].

Caronia et al. [53] presented a novel use of VATS as an alternative to the surgical management of Pancoast tumors which allowed a reduction in the size of thoracotomy, sparing the latissimusdorsi muscle without the need to perform a thoracotomy through the fourth or fifth intercostal space to explore the chest cavity. Combined anterior and posterior

approaches have been performed entirely with video-assistance and without changing the position of patient.

Self-study

1. Which statement is/are true:
   a. Inventor of human laparoscopy and thoracoscopy is Hans Christian Jacobaeus in 1910.
   b. Da Vinci robotic system includes three main components: the surgeon's console (the master component), 3D high-definition vision system and the peripheral effector device (slave component) consisting of 4 arms controlled by the surgeon (one for room control and 3 for the manipulation of mini invasive instruments).
   c. Haptic technology is now being developed, which is a technology of tactile feedback by the user (surgeon) vibrations.
   d. Anterior cervico-thoracic incisions are used for approaching the Pancoast tumors located in front of the anterior scalenus muscle.
2. Which statements are true:
   a. Hemiclamshell incision consists of an antero-lateral thoracotomy usually in the fourth or fifth intercostal space, associated with a partial longitudinal median sternotomy.
   b. Supraclavicular approach for excision of first rib relieves thoracic outlet syndrome by decompression of the brachial plexus in the interscalene region.
   c. Rongeur technique facilitates removal of the entire posterior portion of the rib.
   d. VATS offers an excellent visualization of anatomical structures of thoracic inlet and has been introduced in the diagnosis and treatment of Pancoast tumors.

Answers

1. Which statement is true:
   a. CORRECT.
   b. CORRECT.
   c. CORRECT.
   d. CORRECT.
2. Which statements are true:
   a. CORRECT.
   b. CORRECT.
   c. CORRECT.
   d. CORRECT.

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General Aspects of Thoracic Anesthesia

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Key Points

- Major thoracic surgery and extensive lung resection remain moderate to high risk surgery where outcomes are determined by not only by the quantity of lung and quality of lung function after resection but also by preoperative patient fitness and aerobic performance.
- The implementation of preoperative optimization-collectively termed prehabilitation-enables some high-risk patients previously deemed unsuitable for surgery to undergo curative surgery following a multicomponent intervention regime delivered by a multidisciplinary team.
- There has been an explosion of available airway tubes and devices to implement lung isolation and separation in an effective and safe manner. While DLT are universally used, bronchial blockers are gaining momentum and may reduce minor and major airway injuries. There is increasing use of videolaryngoscopy to facilitate airway management in difficult airway scenarios while fiberoptic bronchoscopy remains the principle diagnostic (and therapeutic) tool to provide visual aid for airway management.
- Ventilation during OLV has recently switched focus from providing oxygenation to defining protective ventilation. Small tidal volumes, recruitment and varying PEEP levels have

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been recently the subject of many studies. However, the exact determinants of protective ventilation have yet to be established.

- Although non-intubated procedures have established a place in our current repertoire, most surgeries still depend on mechanical one lung ventilation.
- A multimodal approach to pain control centered on loco-regional analgesia supplemented with systemic analgesic and low dose opiates is the emerging trend towards enhanced recovery of patients. Although epidurals are the mainstay of postoperative pain relief, there are now many studies favoring paravertebral blocks or truncal blocks to epidurals. Chronic pain remains an unsolved problem with thoracic surgery being a leading cause of postsurgical chronic pain.
- There are high quality large clinical trials underway towards finding definite answers for current paradigms of thoracic anesthesia including the effects of volatile versus intravenous anesthetics, the effect of PEEP on one lung ventilation and lung injury and the dilemma of epidurals versus paravertebral blocks on acute and chronic pain. Outcomes of these studies will determine the future of thoracic anesthesia.

Introduction

Thoracic anesthesia is a highly versatile, dynamic and technically skilled subspecialty providing perioperative care for a moderate to high risk surgery involving the chest and lung. Traditionally, these surgeries involved a large thoracotomy incision, surgical pneumothorax, extensive pleural and lung parenchymal dissection and resection of either segmental or lobar lung parenchyma causing nociceptive stimuli at multiple intercostal and pleural levels. Our specialty evolved over the last century and recent decades to provide sophisticated perioperative solutions for preoperative patient risk stratification for these invasive surgeries to ensure that patients can tolerate intraoperative physiological and surgical stresses and to facilitate postoperative recovery and to ensure acceptable medium- and long-term clinical outcomes and quality of life. We have adopted various general anesthesia solutions for safe induction and maintenance of anesthesia, various alternatives for intubation, airway control and management of pneumothorax with adequate gas exchange during two and one lung ventilation. We have developed and employed a balanced multimodal approach for postoperative pain control with a combination of

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regional anesthesia, systemic use of opiates and multiple analgesics. Despite these efforts, major thoracic surgery remained a high-risk operation with significant pulmonary and systemic pulmonary complications requiring intensive and high dependency care, significant hospital resource utilization and associated cost and suboptimal patient recovery and long-term complications including chronic pain and suboptimal quality of life [1–3].

Parallel to developments in other major surgical subspecialties, thoracic surgery has also witnessed a spectacular trend towards minimally invasive surgical approaches in the form of Video-Assisted and Robotic-Assisted Thoracic Surgery (VATS and RATS, respectively). These surgeries have dramatically reduced surgical trauma and its postoperative sequelae whilst allowing major curative surgery in high risk patient populations for whom thoracotomy was contraindicated; thereby pushing the boundaries of perioperative care [4–6]. These developments together with shorter acting anesthetic agents allowed the establishment of Fast Track and Enhanced Recovery protocols (REF). Nevertheless, there are remaining challenges associated with significant pain that results from a consequence of multiportal incisions and the requirement for postoperative chest drains. Finally, the advent of uniportal VATS technologies with single intercostal incision augmented with surgical blocks has paved the way for ultrafast recovery approaches and complete re-evaluation of our general thoracic anesthetic, intubation and mechanical OLV concepts with a move towards non-intubated VATS managed by spontaneous breathing with sedation or monitored anesthesia care (MAC) [5, 7]. The ultimate goal of these non-intubated procedures is to minimize the adverse effects of tracheal intubation and general anesthesia, i.e. intubation-related airway trauma, ventilation-induced lung injury, residual neuromuscular blockade, and postoperative nausea and vomiting. While such trend may superficially indicate the less active involvement of the thoracic anesthesiologist, just as in any other minimally invasive surgical situation, the role of anesthesia is actually heightened and more intense in terms of patient selection, physiological and clinical monitoring and technical ability to promptly and safely convert to more invasive surgery generally under forced circumstances and sometimes in emergency situations.

Thus, thoracic anesthesia has evolved to meet the demands of a spectrum of new surgical approaches. Parallel to the intraoperative management we are also intimately involved in the entire patient pathway from preoperative evaluation and risk assessment to enhanced postoperative recovery.

Preoperative Evaluation and Risk Assessment

The main goals of preoperative evaluation of thoracic surgical patients, especially those who present for lung resections is (a) to predict if they can cope with one lung ventilation (OLV) during surgery and their postoperative dyspnea, (b) to provide prognosis for postoperative mortality, pulmonary and systemic complications and (c) to ensure that they will have a reasonable quality of life after removing their lung lobe(s). Depending on this evaluation the patients may be offered curative lung resection, but high-risk patients could only be offered less invasive surgery or even declined for surgical considerations. Hence, preoperative patient evaluation is crucial for risk assessment and for planning the best perioperative pathway [8–11]. Moreover, it is important to identify if any of the risk factors are modifiable as this would provide an opportunity for risk reduction by means of preoperative optimization [1, 2, 12]. Preoperative assessment of patients scheduled for thoracic surgery comprises 5 main areas including 1. Evaluation of comorbidities, 2. cardiac risk assessment, 3. mechanical respiratory function, 4. diffusing lung capacity and 5. cardio-pulmonary reserve.

a. Evaluation of comorbidities

Preoperative assessment is influenced by many factors and comorbidities [8, 13, 14]. Age, obesity, smoking and alcohol abuse are independent

predictors for postoperative complications. Likewise, diabetes, malnutrition and reduced kidney function appear to increase the perioperative risk. Most of these factors are included in preoperative risk assessment scores such as the Thoracoscore and the Eurolung scores although the predictive value of these is less evident compared to those used for cardiac operations.

b. Cardiac risk

Cardiac risk assessment is performed according to cardiovascular evaluation guidelines for non-cardiac surgery [15]. The Thoracic Revised Cardiac Risk Score (ThRCRI) stratifies patients into low, intermediate and high risk [16, 17]. Cardiology consultation is needed for ThRCRI > 2 and in cases of a newly suspected cardiac condition. In addition, physical performance and functional capacity has become a key parameter in preoperative risk stratification since a low level of aerobic fitness is highly predictive of early mortality and morbidity as well as prolonged hospital stay following major surgery [8, 13, 14]. The patient functional capacity and physical fitness can be qualitatively estimated based on Metabolic Equivalents of Task (METs) using self-report questionnaires such as the Duke Activity Status Index or by using simple instruments (accelerometer, pedometer) [18]. One MET is defined as the amount of energy expanded or oxygen consumed (VO_2) at rest. The relative mortality increase of approximately 10% for every 1 MET decrement in exercise capacity or reduced functional capacity mandates that patients with significantly reduced METS are referred for cardiology consultation. Beyond these qualitative measures, biomarkers of cardiac function such as BNP or pro-BNP have also been suggested as useful predictors for cardiovascular risk assessment [13]. However cardio-pulmonary exercise test (CPET) has emerged as the gold standard for the evaluation of patients with decreased cardiac reserve (see below).

c. Mechanical respiratory function

Pulmonary function tests (PFTs) permit the evaluation of mechanical respiratory function. FEV1 and FVC are the most important parameters used for respiratory risk assessment. For instance, the British Thoracic Society 2001 guidelines suggested absolute preoperative FEV1 of 1.5 L for lobectomy and 2 L for pneumonectomy as selection criteria for surgery. However, these recommendations may not be applicable to all ages, builds, races, and genders without normalisation. Values calculated as a percentage of the normal predicted value correlate better with the outcomes. In particular, percentage of predicted postoperative values (%PPO) (ppoFEV1 and ppoFVC) are useful to appraise the potential effect of surgery on postoperative respiratory outcomes although these also have limitations. Nevertheless, there is general consensus that patients with ppoFEV1 > 80% are at low risk for postoperative complications (REF). Patients with ppoFEV1 values between 40–80% need further evaluation in conjunction with ppoDLCO. Low ppoFEV1 values (30–40%) do not necessarily preclude surgery but have to be carefully evaluated with ppoDLCO and cardio-pulmonary exercise testing.

d. Diffusing lung capacity

Diffusing lung capacity is the ability of the lungs to transfer gas from inhaled air to the blood. It is evaluated through the study of carbon monoxide diffusion capacity (DLCO). Like pulmonary function tests, the percent predicted postoperative DLCO is adopted for risk assessment before lung surgery. Patients with ppoDLCO > 80% are considered at low risk for postoperative respiratory impairment. ppoDLCO values below 60% must be evaluated considering also ppoFEV1 and, eventually, submitting patients to CPET. Some authors suggest 40% as low limit for DLCO.

Beyond lung function testing, arterial blood gas analysis also appears useful in preoperative risk assessment in as much as severe hypercapnia or hypoxemia are risk factors for prolonged postoperative ventilation and pulmonary complications and thus, inform against major lung resection.

e. Cardio-pulmonary reserve

Patients with reduced cardiac or respiratory reserve should be assessed with cardio-pulmonary

tests. CPET aims to evaluate the capacity of both cardiovascular and respiratory system to sustain a physical effort. CPET provides information on aerobic fitness through several data plots i.e. maximal oxygen consumption (VO_2max), maximum minute ventilation (MMV), anaerobic threshold (AT), peak heart rate, respiratory gas exchange ratio and minute ventilation to carbon dioxide output ratio (VE/VCO_2) [13, 14, 19].

Patient with VO_2max > 20 ml/kg/min are regarded to be at low risk and are deemed fit for major surgery [8, 9]. Patients having a VO_2max between 10 and 20 ml/kg/min are at moderate risk and require multi-dimensional evaluation comprising ppoFEV1 and ppoDLCO values. Recently, the VE/VCO_2 slope has been suggested as good predictor of postoperative outcome in this subgroup of patients. A VE/VCO_2 slope value > 35 is considered predictive for postoperative complications. Patients with VO_2max < 10 ml/kg/min are regarded as high risk for poor postoperative outcome and should be considered for minimally invasive procedure or non-surgical options.

Lower technology tests (six minutes walking test—6MWT, stair climbing test—SCT and shuttle walk test—SWT) may be used in hospitals where CPET is not readily available [8, 14]. Their use has been suggested in intermediate risk patients to exclude the need for CPET that is more complex and time consuming. Further investigations are required to elucidate their effective role in this context.

Preoperative Optimization, Prehabilitation

Postoperative recovery after major thoracic surgery can be impeded by the development of organ dysfunction and major complications. These develop increasingly among patients with cardiovascular and chronic pulmonary diseases, but they are also influenced by general life-style factors such as smoking, excessive alcohol intake and systemic conditions such as nutritional defects, anemia and frailty. Enhancing the functional capacity of an individual before an operation to enable him or her to withstand the stress of surgery, has been coined "prehabilitation" [13, 20, 21]. The principle promise of thoracic prehabilitation is twofold. Firstly, to potentially improve clinical outcomes by increasing the number of patients deemed suitable for curative lung cancer surgery and secondly, by reducing efficiently the occurrence and severity of complications and enhancing the recovery process of those who undergo surgery.

a. Psychological support

Negative feelings and thoughts, anxiety, depression and catastrophizing before surgery may affect outcomes after surgery [22]. Negative emotions can enhance pain sensations and modify behavior especially those related to adherence to physiotherapy and medication intake and return to usual activities [23]. Stress also has effects on the surgical inflammatory response and wound healing. It is therefore logical to think that psychological interventions that try to reduce negative emotions and promote optimism, conscientiousness and emotional stability could have a positive influence on postoperative outcomes [22]. However, there has been a longstanding controversy about whether psychiatric and psychological treatments improve the survival of patients with cancer.

b. Education and counselling

Patients and their next of kin should be instructed by dedicated health care professionals trained in education therapy. These important messages should be reemphasized at the preoperative visit by the surgeon, anesthesiologist and the physiotherapist by highlighting preoperative medical assessment, general nutritional and lifestyle recommendations, description of the surgical and anaesthetic procedures and the key steps in postoperative care.

c. Smoking cessation

Smoking is a modifiable risk factor for postoperative complications, specifically pulmonary postoperative complications. Indication of surgery due to lung cancer may be a suitable

motivation for patients to stop smoking. Such recognition could be enforced by intensive behavioral support and pharmacological interventions. Pharmacotherapy including nicotine substitution, varenicline, and bupropion treatment is indicated in nicotine dependent patients (those smoking within 30 minutes of waking, >10 cigarettes/day, history of withdrawal symptoms in previous weaning). Smoking should ideally be stopped at least 4 weeks before surgery to maximize the pulmonary benefits of smoking cessation, but curative surgery should not be significantly postponed as this could lead to cancer progression.

d. Nutrition

Malnutrition and loss of muscle mass are frequent in the preoperative period and have a negative effect on clinical outcome as a result of inadequate food intake, low level of physical activity and catabolic derangements associated with chemotherapy in lung cancer patients [3]. Therefore, all patients should be screened for malnutrition before lung surgery and optimization of their perioperative nutritional status may be helpful in decreasing postoperative complications. The Malnutrition Universal Screening Tool is a useful screening tool to identify adults, who are malnourished, at risk of malnutrition (undernutrition), or obese. In cases where severe malnourishment is present (weight loss > 10%, body mass index <18,5 kg/m^2 or serum albumin <30 g/L) a multidisciplinary approach is needed, as patient may benefit from delaying the surgery to supplement nutrition and improve overall status [24]. Protein intake should also be specifically assessed, particularly patients attending to prehabilitation or pulmonary rehabilitation with exercise training as they have higher dietary demand.

e. Alcohol abstinence

Since alcohol abuse has been identified as an independent risk factor for primary acute lung injury after lung cancer resection, preoperative abstinence may help to modify to some extent the pathophysiological processes seen among alcohol abusers. Preoperative abstinence has been shown to significantly reduce the incidence of arrhythmia in the postoperative period and improve immune control, measures of coagulation and the neuroendocrine stress response. Intensive alcohol cessation interventions include patient empowerment, with detailed information and recommendations regarding prophylaxis/treatment of alcohol withdrawal for at least 4 weeks before the surgery.

f. Oral hygiene

There are various considerations for cancer patients regarding periodontitis, odontogenic foci, and colonization of dental plaque by Gram-negative bacteria towards biofilm formation that constitutes a reservoir of respiratory pathogens. Under anesthesia and following mechanical ventilation these patients are at increased risk for dissemination of oral bacteria into the upper respiratory tract and postoperative infections. Based on results from other surgical fields and large-scale observational studies, more attention should be paid to improved preoperative oral care including chlorhexidine mouth rinsing or increased efficacy of toothbrushing protocols.

g. Improving physical fitness

Results from multimodal rehabilitation training conducted over 6 to 12 weeks demonstrate improved exercise tolerance and quality of life in different patients including those with COPD. Adopting these potential benefits to the highly motivated preoperative period represents a window of "therapeutic opportunity" for effective prehabilitation. Several hundreds of thoracic patients have been part of larger prehabilitiation RCTs evaluating exercise programs prior to major surgeries and the effectiveness of respiratory muscle training (deep breathing, vital capacity maneuver, diaphragmatic and abdominal muscle exercise), endurance training (cycloergometer, treadmill) or a combination of both which was evaluated compared with usual care [21]. While training sessions varied in duration (from 6 to 45 hours), intensity and were applied over different time frames (1 to 4 weeks) before surgery, the data seem to support favorable clinical and functional effects [21]. Specifically,

there were fewer occurrences of pulmonary complications and shorter hospital length of stay in association with improved aerobic fitness and increased inspiratory muscle strength. However, prehabilitation did not reduce perioperative mortality and cardiovascular complications rate.

In summary, prehabilitation is an attractive concept especially for higher risk thoracic surgery judged by inclusion in recent ERAS guidelines with relatively strong recommendations and current engagement of the thoracic anesthesia community towards more precise and definite clinical studies and multidisciplinary programs.

Inhalational Versus Total Intravenous Anesthesia (TIVA) for Thoracic Surgery

Induction and maintenance of general anesthesia can be achieved with an inhalational approach using volatile agents such as sevoflurane, isoflurane or desflurane or by a total intravenous concept usually with target-controlled infusion of propofol and an opiate such as remifentanil or fentanyl.

From a historic and physiological perspective, TIVA was recommended during one lung ventilation to avoid the inhibition of hypoxic pulmonary vasoconstriction by some of the classical inhalational anaestheitics, however this is less pronounced with usual doses of "modern" inhalational anaesthetics. There are also a variety of arguments including basic science, in vitro studies and variable patient cohort studies that anesthesia protocols may provide direct or indirect organ protection and immunomodulation. Most of these studies have favored inhalation anesthesia for pre and postconditioning after biological insults such as ischemia reperfusion injury.

For instance, the Madrid group has investigated the effects of sevoflurane compared with propofol on the incidence of pulmonary complications in patients undergoing thoracic surgery in a single center RCT [25]. PPCs were higher in the propofol group (28.4% versus 14%), together with increased systemic and pulmonary cytokine levels. However, there was no associated increase in critical care stay, hospital stay, or 30-day mortality.

This issue was also explored in a multicenter RCT lead by the Basel group to compare the effects of a volatile agent (desflurane) versus an intravenous anesthetic (propofol) [26]. The trial enrolled 460 patients in 5 centers with a good (approx 40%) representation of major thoracotomy approaches. There was no difference in major complications during hospitalization and within the first 6 months after surgery between these interventions. Such results seem to suggest equivalence of these regimens in anesthetic management of general thoracic surgery.

One area where the opposite hypothesis is pursued relates specifically to cancer surgery and to potentially long-term effects of intraoperative anesthetic agents. According to this major argument, the anesthetic agents may differentially affect the surgical stress response and intracellular cancer cell signaling which in turn might promote progression of minimal residual disease or creation of a premetastatic niche that traps circulating tumor cells, leading to clinical cancer recurrence and diminished long-term survival [27]. For instance, the cytoprotective effects of inhalational anesthetics when applied to cancer cells together with their effects on immunosuppression may facilitate the development of a pro-malignant environment that supports the growth of residual cancer cells. While this topic is mainly pursued in the general cancer field, it is also relevant to lung cancer resection and thoracic anesthesia.

However, one retrospective study focusing on non-small cell lung cancer patients showed no better benefit for a propofol-based TIVA approach, when compared to inhalation agents on long-term oncologic outcomes after lung resection [28]. This current controversy over an optimal anesthetic management for lung cancer surgery will be investigated in a well-designed large multicenter trial alongside colon cancer in the near future (VAPOR-C trial).

Lung Separation, Isolation and Airway Management

a. Goals and Definitions

Airway management and lung isolation is one of the core principles of thoracic anesthesia to facilitate diagnostic and therapeutic procedures on the chest and lung by differential ventilation. The overall objectives are to secure the airway and promoting collapse, surgical exposure and immobility of the operated nondependent lung while maintaining adequate gas exchange by the ventilated and dependent other lung. Such airway management frequently requires lung separation in order to prevent contamination of a healthy lung with pus, blood or other fluids from the affected contralateral lung and to isolate one lung in unilateral thoracic disorders. In the current terminology, ***separation of the lungs*** reflects a complete "anatomical" seal with a double lumen tube (DLT), and the ***isolation of the lung*** means a "functional" (but potentially incomplete) sealing with generally a bronchial blocker (BB).

b. Indications

There are some recognized *absolute indications for lung separation* in which a protective strategy for the contralateral lung is needed, including potentially life-threatening conditions such as: massive pulmonary bleeding, pneumonia with pus, broncho-pleural and broncho-cutaneous fistulae, as well as giant unilateral bullae. Maintenance of adequate gas exchange, prevention of soiling/flooding the other lung with contaminated material/blood and avoidance of barotrauma are best achieved with DLTs in these situations [29]. Some surgical interventions as sleeve pneumonectomy, or bronchopulmonary lavage for alveolar proteinosis or lung transplantation for infective etiologies such as cystic fibrosis also require lung separation with a DLT. Some high priority operations with relative indications also favor isolation with DLT such as pneumonectomy, sleeve resection on the bronchial mainstem or thoracic aneurysm operation with cardiopulmonary bypass. In all the other situations with relative indications including interventions on the pleura and mediastinal structures, lobectomies and lower degree resections, oesophagectomy, orthopedic surgery on the chest, thoracic spine surgery, minimally invasive cardiac surgery lung isolation could be employed either by DLT or BB [29–31].

The major advantage of BBs is that they are placed through a conventional SLT. In emergency situations, securing the airway is a priority and this is performed easier and faster with an SLT. Moreover, in patients with abnormal airway anatomy (post-laryngeal/pharyngeal surgery, tracheotomy), or predicted difficult intubation as well as in singers and children BBs are most suitable for lung isolation. In addition, SLT and BBs offer advantages in situations where postoperative ventilation is planned or needed, as there is no additional need for the potentially risky replacement of the DLT by an SLT using an airway exchange catheter.

c. Comparing DLTs and BBs

Modern DLTs have a fixed curvature and lack a carinal hook, in order to avoid airway laceration and kinking. They are available in various French sizes from 28 to 41 sharing similar features but modified cuff shape and location. A colored bronchial cuff, commonly blue, permits its easy identification by fiberoptic bronchoscopy. The right endobronchial cuff is donut-shaped and allows the right upper lobe ventilation slot to ride over the right upper lobe orifice. Many anesthetists prefer using only left sided DLT to avoid potential misplacement of the right sided DLT and obstructing the right upper lobe bronchus. It is essential to select the properly sized DLT and place it correctly anatomically and to an optimal depth. The most accurate method to select a left-sided DLT size is to measure the left bronchus width and the outer diameter of the endobronchial lumen of the DLT. The largest tube that would fit safely to that bronchus can then be selected. This method is less validated for right sided DLT but it is a widely held and general view that a 37

French DLT can be used in most adult females, while 39 French can be used in the average adult male. However, this must be individualized as undersized DLT may not provide sufficient isolation and oversized DLTs could led to serious airway complications, including tracheo-bronchial rupture. The optimal depth of insertion for a left-sided DLT is strongly correlated to the patient's height. In general, the depth of insertion for a DLT should be between 27 and 29 cm at the marking of the incisors. An inadvertent deep insertion of a DLT could lead to rupture of the left main stem bronchus or unilobar ventilation.

There are different types of BBs currently available for modern clinical practice [29–31]. They are generally of size 9 French BBs with different steering mechanisms and a patent channel of 1.4–2 mm size to facilitate the collapse of the lung and/or oxygen insufflation. The Arndt blocker is also available in smaller sizes (5 and 7 French) and uses a wire-guided mechanism. The Cohen blocker is equipped with a rotating wheel that allows flexing the tip of the blocker to facilitate positioning in the desired bronchus. In contrast, the Uniblocker has a fixed curve similar to a hockey stick that is positioned by applying the correct rotation. The EZ-blocker is designed with a Y shaped bifurcation with a bronchial cuff engineered on each distal end that enables placement of a cuff beyond the main carina in both main bronchi allowing isolation of either lung and selective or sequential deflation [32].

Several RCTs including nearly a thousand patients have compared intubation and lung isolation with DLTs versus BBs [33]. Generally, the time required for initial insertion and for lung collapse as well as the success rate for proper position and the quality of surgical exposure have been rated quite similarly between the techniques. Lung collapse can be facilitated by applying a period of disconnection from the ventilator circuit before inflating the BBs balloon and by intermittent suction through the channel of the BB. Perhaps the most important limitation of BBs has been the more frequent displacement that occurs during extensive surgical manipulations and challenges to reposition the blocker with the patient in the lateral position.

In contrast, airway complications such as transient sore throat (10–45%), hoarse voice (15–25%) and irritative cough appear more frequent with DLTs than with SLTs combined with BBs [34]. Likewise, a higher incidence of mucosal damage and hematoma has been observed within the larynx and the trachea-bronchial tree following the utilization of DLTs versus BBs [35, 36]. Anecdotal cases of rupture of the trachea-bronchial membrane have been related to placement of an oversized DLT or keeping the stylet in place whilst attempting to guide the endobronchial tip into the mainstem bronchus.

d. Utilization of bronchoscopy

Flexible bronchoscopy (FOB) represents one of the most important technical skills and diagnostic modality for thoracic anesthesia; aiding correct airway device placement and rapidly diagnosing malpositions [37]. While many anesthetists practice blind placement of left DLT, which could be confirmed by routine clinical evaluation based on chest movement and auscultation, reposition is required in a large fraction of blind insertion following FB examination. Alternatively, left DLT placement can be directed using FB whereby advancement of the DLT through the trachea following intubation is directly visualized and the bronchoscope is used as a guide over which the DLT is railroaded.

A complete fiberoptic examination of the left DLT include confirmation of the main carina landscape from the tracheal lumen of the DLT. This should ensure clear visibility of the tracheal mucosa, anatomy and tracheal carina; confirming the unobstructed opening of the right main bronchus, passage of the DLT in the LMB, evaluation of the correct depth of the DLT by visualizing the top of the bronchial cuff 5–10 mm below the carina. FOB can also evaluate any bronchial mucosal damage or bleed and that the tracheobronchial tree is free of secretions. In addition, examination from the bronchial lumen should confirm the relative position of the tip of

the DLT in relation to the bifurcation of the left lower and upper lobe and segmental analysis of these lobes. Finally, if a transparent tube is used, pulling back the bronchoscope in the bronchial lumen allows a different visualization of the tracheal carina and the relative position of the proximal portion of the bronchial cuff and the black radiopaque line.

FOB is a must for positioning a right sided DLT and BBs. Indeed, most anesthetists utilize FOB to direct advancement of the right DLT beyond the tracheal carina into the RMB. In this scenario the bronchoscope is inserted into the bronchial lumen of the right DLT and the scope is positioned in front of the bronchial tip of the DLT. Initially, the origin of right upper lobe (RUL) bronchus is identified as well as the anatomy of the right bronchial tree prior to placing the DLT into the proximal RMB. Subsequently, the FOB is positioned in front of the RUL bronchus origin and the DLT is advanced over the FOB maintaining its orientation. The lateral opening of the DLT (Murphy eye) is than identified and its alignment with the opening of the RUL is confirmed. Once this relationship is achieved the bronchoscope is then advanced distally to the intermediate bronchus through the distal opening of the DLT to confirm the non-obstruction of the middle and lower lobe bronchi. Reintroduction of the bronchoscope in the tracheal lumen of the right DLT completes the FOB examination and allows visualization of the carinal landscape and the bronchial cuff ensuring adequate seal of the right MSB and absence of herniation of the cuff into the trachea or the LMB.

Alternatively, it is also possible to fully position the DLT blindly and to confirm the position with FOB after the blind insertion, however in this situation orientation and confirmation of the correct positioning maybe more challenging.

Regardless of optimal initial tube placement following intubation, tube position may change any time the patient is mobilized and following various surgical manipulations. Desaturation and sudden changes in airway pressures or lung compliance should prompt immediate check with FOB. A quick look at the carinal landscape should immediately help diagnosing displacement of the DLT into the distal trachea or herniation over the carina. Moreover, distal movement of the bronchial cuff away from the tracheal carina should raise the suspicion of lobar intubation. FOB through the bronchial lumen should then be used to verify and optimize the DLT position. With the left DLT this should ensure unobstructed view of the upper and the lower lobar bronchus. With a R-DLT, the end point of correct positioning should be the complete or at least partial alignment of the Murphy eye portion of the bronchial tip at its lateral opening and the origin of the RUL bronchus.

FOB is also essential in the placement of BBs. With the Arndt blocker The Arndt BB the retractable guide with its distal loop wire should be secured over the FOB once the two devices are passed through their specific parts of the multiport connector. This unit is then inserted into the SLT and the advancement of the BB and its placement into the desired mainstem bronchus is guided by the FOB. Removal of the retractable guide loop and inflation of the BB is then confirmed under direct visualization. Similarly, FOB also aids the progression, correct positioning and inflation of the Cohen and other BBs.

e. Utilization of videolaryngoscopy (VL)

VLs have several potential roles in lung separation for thoracic surgery including placement of a DLT in patients with predicted or unanticipated difficult airway or facilitating exchange of a SLT for a DLT following an initial intubation with a SLT. Finally, in special circumstances, intubating the trachea is achieved using a SLT with a bronchial blocker advanced alongside the SLT under VL-guidance.

VLs provide a better laryngeal view without the need for airway alignment for endobronchial intubation with double lumen tubes (DLTs). VL-assisted DLT intubation is associated with improved glottic visualization, however, that does not readily translate into easier tracheal intubation. A recent meta-analysis has shown that, compared with the direct laryngoscopy, the VLs provided a higher success rate at first attempt for DLT intubation, a lower incidence

of oral, mucosal or dental injuries and postoperative sore throat, and comparable intubation time [35].

The three main classes of VL include the angulated-blade VL, those with a guidance channel that facilitate DLT guidance into the trachea, and video-stylets, however the performances are likely to be different between these devices.

The performance of both channeled and non-channeled VLs appear superior to the direct laryngoscopy in terms of improved glottic visualization and success rate in obese patients, however, the intubation time is generally longer with the non-channeled VLs [36]. Compared with the angulated-blade VLs, the channeled VLs are equipped with thinner blades and pronounced curvature that make them useful in patients with limited mouth opening and restricted neck movement.

f. DLT and SLT with embedded camera.

New airway devices became available during the last decade that have incorporated a high-resolution LED camera to SLTs and left side DLT. The main advantage of these tubes is the continuous visualization of the airways. The disadvantages of these devices are that they are significantly larger and that there is the possibility of vision loss or fogging in the presence of abundant secretions or bleeding.

g. Airway exchange

The vast majority of patients undergoing thoracic surgery are extubated at the end of surgery. However, after complicated or prolonged surgery, some patients require postoperative ventilation. In many of these patients changing the DLT to a SLT is low risk, however long surgery with the potential of significant airway edema or difficult initial intubation mandates the use of airway guides or exchange catheters to facilitating safe exchange and maintaining the airway during this procedure. The airway guide may be used for inserting an SLT over a DLT and vice versa, or simply inserting a difficult tube. There are several tube exchangers available with variable length and size with depth is clearly marked and are easily adapted for either oxygen insufflation or jet ventilation. The following details should be kept in mind in order to minimize risk of airway injuries: 1. The size of the airway guide and the size of the DLT must be determined and should be tested outside the patient before the use of the airway guide. 2. The airway guide should never be inserted against a resistance as this may result in perforations of the tracheobronchial tree. 3. The anatomy of the supraglottic tissues should be optimized when passing the tube over an airway guide and this is best achieved by laryngoscope or VL once the guide is properly positioned in the trachea. 4. A mode of jet ventilation should be immediately available in case placing the new tube over the airway guide into the trachea proves to be difficult.

h. The predicted and unanticipated difficult airway

As discussed above, a predicted or encountered difficult airway remains a major challenge for the thoracic anesthetists for two main reasons. Firstly, intubating with the DLT in this situation is likely to be technically challenging and secondly, the risk of both minor and severe airway injuries may be greater in patients with a difficult airway [38, 39].

The priority is just in any other anesthetic situation is the provision of a secure airway, typically with a SLT. After this is achieved the principle dilemma remains whether or not lung separation is truly required for absolute indications. In this rarer scenario, the best option is to use of an exchange catheter and exchanging the SLT to an appropriate DLT using every possible aid such as VL for safe and atraumatic exchange. However, for most surgeries and relative indications BBs represent the best safe alternative for difficult airway management when OLV is indicated. An added advantage of the BBs for such lung isolation that they can be deployed through any type of airway of an adequate luminal size even in situations where placing a SLT is difficult.

General Aspects of Thoracic Anesthesia

a. Positioning and protection of pressure points

The majority of intra-thoracic surgeries require lateral positioning of the patient for optimal surgical exposure and breaking the operating table to optimize surgical access to the thoracic cavity is common practice. If unprotected, such position may lead to serious neurologic and vascular complications.

Special attention needs to be paid to the cervical spine, arm and leg positioning and sensitive areas should be protected by appropriate padding or other measures. The cervical spine should be stabilized in near neutral position since an excessive lateral flexion may cause a "whiplash" syndrome. Overextension or too much flexion of the cervical spine may also impact on the tracheobronchial tree and dislodge the DLT or BB back to the trachea or force the tube into lobar bronchi. Eyes and ears should be protected against any pressure injury. Padding should also be placed under the thorax to keep the weight of the upper body off the dependent brachial plexus. Attention should also be paid to the upper non-dependent arm when installed on the arm support or rested on the dependent arm with gel pads positioned between them to avoid any vascular or nerve compression. The defendant leg should be slightly flexed, and padding used to protect the peroneal lateral nerve. A pillow should also be placed in between the legs to prevent any pressure compression, especially in a paralyzed state. While the strapping over the hip should be reasonably secure for its purpose, it is essential to avoid compression of the sciatic nerve.

b. Fluid management

There is strong evidence that perioperative fluid administration influences postoperative outcomes. Reports from the 80s and 90s suggest that positive postoperative fluid balance resulted to increase the risk for acute lung injury especially in major lung resection (i.e., lobectomy, pneumonectomy). The pathophysiologic mechanism underlying postoperative lung injury is multifactorial and, from this point of view, related to fluid overload, reduced lung lymphatic drainage, and pulmonary endothelial damage. While fluid restriction may have beneficial effect on lung injury, it may compromise circulating volume, cardiac output and could contribute to organ hypoperfusion and dysfunction. The development of acute kidney injury (AKI), myocardial ischemia and cognitive dysfunction, delirium are primary concerns [3, 40–42].

A discussion on fluid management of patients scheduled for thoracic surgery should consider 1. Intraoperative fluids therapy regimes, 2. The type of administered fluids and c. postoperative fluid therapy regimes.

Intraoperative fluid therapy:
Hypervolemia shall be avoided in order to decrease the risk of acute lung injury. A fluid restrictive approach has been advocated for thoracic patients, but it should not reach critical hypovolaemia and compromise non-pulmonary organ function. Keeping the lung dry and the circulatory compartment close to normovolemia remains a wise statement that has been advocated for several decades and can be achieved by the "near-zero balance" concept.

An intraoperative administration of maintenance fluids of 1-2 ml/kg/h seems adequate to counteract the basal evaporation rate from airway and skin during surgery. This aspect is also mitigated by the reduction of preoperative fasting according to guidelines and allowing clear and sugary fluid uptake until 2 hours prior to surgery. It also should be kept in mind that intraoperative hypotension may have an important vasoactive component in addition to volume status and administration of vasopressors could be helpful to counteract the anesthetic-induced vasorelaxation and to convert the relative hypovolemia into normovolemia.

A goal directed fluid therapy has been considered and would likely to be attractive, but

its implementation is thoracic surgery remains challenging [41]. Dynamic indices (i.e. pulse pressure variation and stroke volume variation) are not reliable in open chest condition. Cardiac output measured with both calibrated and non-calibrated monitors can be used to manage intraoperative hemodynamics. Extra-vascular lung water index (ELWI), obtained with transpulmonary thermodilution method, must be interpreted with caution because it may be overestimated after resection of the lung. Also, transesophageal doppler monitoring may be useful to guide fluid therapy and hemodynamic management in lung surgery. Finally, hemoglobin level may be useful to evaluate the volume status.

Type of administered fluids:
Balanced crystalloid solutions are preferred over sodium chloride solutions to avoid hyperchloremia and hypernatremia. Normal saline solution may be considered for the correction of electrolytes disorders. Hydroxyethyl starch must be avoided as routine fluid therapy and reserved for severe bleeding cases. Its use has been related to acute kidney injury both in critical and surgical patients.

Postoperative fluid therapy:
Postoperative fluid administration should be based on minimal intravenous infusion (1 ml/kg/min) and liberal oral water intake. Urine output does not represent the volemic status and should not be used as main parameter to guide fluid administration in the early postoperative phase. The fast recovery to normal feeding is also useful to maintain the euvolemic state.

In summary, the thoracic surgical patient should receive an individualized fluid management plan that considers his co-morbidities and the operative complexity. Any perceived pulmonary protection by fluid restriction should be balanced by the ever-existing potential for negative hemodynamic effects. A zero-balance fluid approach can be applied with balanced salt crystalloid and be part of the enhanced recovery program [41]. The clinicians should maintain a close observation of ongoing fluid losses (in/out fluid balance) and maintenance of vital signs not only intraoperatively but even more during the postoperative period. Advanced cardiac monitoring of the central circulation and end organ perfusion (cerebral oxygenation by near-infra-red spectroscopy) and/or central venous oximetry are valuable adjuncts but should be reserved for high-risk patients and complex procedures.

One Lung Ventilation

The unphysiologically nature of OLV has been established for decade with the consequences of hypoventilation, ventilation/perfusion mismatch, and intra-operative hypoxia [43, 44]. Furthermore, OLV is associated with PPCs in approx. 20% of patients, including post-thoracotomy mild ARDS. This phenomenon is linked to Ventilation Induced Lung Injury predominantly affecting the ventilated and dependent lung during OLV and there is debate regarding the contribution of the various components of VILI such as volutrauma, barotrauma and atelectotrauma in the setting of OLV [45].

Tidal volume has been a principle component of injurious and protective ventilation strategies ever since it has been shown that lower tidal volumes conferred significant clinical benefits in ARDS. Lung protective ventilation with low tidal volume (VT) and moderate-to-high levels of PEEP has shown to reduce PPCs even when applied in the operating room for short periods of time in patients with healthy lungs [46–50]. Support for these suggestions stems from small single-center studies or comparing new strategies with historical controls and there is no consensus regarding what constitutes “low or high VT” during OLV. Our recent meta-analysis demonstrated that application of a low VT (4–6 mL/k) was associated with some clinical benefits compared to high tidal volumes (8–10 mL/kg), in terms of reducing pulmonary infiltrates and reported incidence of mild ARDS. However, these benefits did not translate into reduction of broader PPCs or altered hospital length of stay [51].

Beyond the controversy regarding low VT during OLV, there is even more some dispute about the benefits of PEEP in reducing PPCs. A recent study found that low tidal volumes is protective as long as an adequate level of PEEP is applied [52]. However, the level of adequate PEEP during OLV remains controversial and as a consequence, "moderate" levels of PEEP have been used in order to minimize undesirable effects, mainly the appearance of intrinsic PEEP and alveolar overdistension [44, 45] Ferrando et al. explored the issue of optimal PEEP by means of an individualized evaluation looking for the level of PEEP that is associated with the best compliance within an open lung approach, following an alveolar recruitment maneuver [53]. In this study the mean value of PEEP was 8 ± 3 cm H_2O.

The search for the principle determinants of injurious mechanical ventilation has united the concept of low tidal volume and PEEP by demonstrating that the benefits of protective ventilation was related to driving pressure more than any other ventilatory parameter [54]. This concept is being applied to perioperative medicine including thoracic anesthesia. An individualized open-lung approach (OLA) by using low tidal volume (VT 5–6 ml/kg PBW) and individualized PEEP with recruitment maneuvers, decreased the driving pressure for a given VT, and potentially increased the protective effect of this strategy and resulted in reduced PPCs [55].

The hypothesis that low DP during OLV is associated with fewer PPC has been tested in a recent RCT. This study employed driving pressure–guided ventilation during OLV that significantly reduced the incidence of PPCs compared with conventional protective ventilation in thoracic surgery [56]. Surprisingly, the median difference of driving pressure between the two groups was only 1 cm H_2O.

These advances provide important new insights into safe conduct of OLV but also leaves many questions unresolved. Thereby the authors suggest a relatively low tidal volume ventilation both during two and OLV and a focus on driving pressure either as a safety threshold (<15 cm H_2O) or by titration. Technically this is best achieved by individualizing PEEP for a given patient by PEEP titration to calculate optimal PEEP. We also recommend application of recruitment maneuvers at critical stages of the surgery such as at the beginning of OLV and prior to extubation.

Currently, a large multicenter trial (PROTHOR) is addressing the impact of a preselected PEEP on outcomes after thoracic surgery, which will likely provide new information on some aspects of the PEEP controversy [45].

Pain Management

a. Multimodal analgesia for thoracic surgery

Professional recommendations and guidelines by various societies promote multimodal analgesia as the most effective strategy to improve pain relief and reduce the side effects of the individual analgesic agent [57]. This multimodal approach is based on a combination of various analgesic agents and/or techniques that target different nociceptive mechanisms. Recent reviews on analgesic care in ERAS protocols report the same concept, highlighting the necessity of combining systemic and loco-regional analgesia to favor opioid-sparing strategies [3, 58]. The latter goal is extremely important, to minimize not only the side effects of this pharmacological class, but also the risk of respiratory complications of patients undergoing thoracic surgery and to attenuate the future opiate dependence of our patients.

b. Thoracic epidural analgesia (TEA)

TEA has long been considered the gold standard technique for pain management after thoracic surgery with ropivacaine 0.2% and levobupivacaine 0.125% being the most popular local anesthetic agents. TEA appears to provide a better pain relief than opioid PCA treatment and promotes recovery. Local anesthetics can

be supplemented with opiates to increase the efficacy of epidural analgesia. However, the invasiveness of TEA and its limitations must be considered including the challenging nature of placement of thoracic epidural catheter, the need for adequately skilled care providers for its perioperative management, and its effects on sympathetic blockade, respiratory depression, urinary retention and, rarely, local complications both during and after procedure.

c. Thoracic paravertebral block (TPVB)

In the context of mini-invasive surgical approaches, such as VATS lobectomy, the TPVB has grown in popularity and it is now increasingly proposed as an alternative to TEA. The acute pain control has been comparable to TEA, but TPVB has been associated with less side effects and an improved safety profile [58, 59]. A recent meta-analysis concluded no difference between these techniques with respect to pain relief, major complications, length of hospital stay and 30-day mortality for patients undergoing thoracotomy [59].

There are several variations of TPVB ranging from single shot PVB to continues infusion after surgical insertion of a PVB catheter under direct vision. Single-shot TPVB was shown to be effective for pain control after VATS in the immediate postoperative period. TPVB is routinely combined with an opioid-based PCA to ensure adequate postoperative pain control.

The TPVB can be performed with the landmark technique, the ultrasound-guided approach or intraoperatively by the surgeon but their relative accuracy, efficacy and safety has not been fully established. The TPVB is easier and safer than TEA to perform, but it is not devoid of potential complications such as pneumothorax, hemodynamic compromise, or total spinal anesthesia.

d. Intercostal nerve block (ICNB)

ICNB is a well-known, fairly simple technique for pain management after thoracotomy [45]. Both the single-shot technique and the continuous infusion are possible, with the latter being more effective after thoracic surgery.

e. Serratus anterior plane block (SAPB)

The SAPB was originally proposed for breast surgery but its applications have later been extended and is now often used in thoracic surgery. It is an ultrasound-guided thoracic wall nerve block that covers the lateral cutaneous branch of the intercostal nerves from T2 to T9. The SAPB provides more hemodynamic stability compared with TEA after thoracotomy and potentiates PCA analgesia reducing pain and morphine consumption. The limited invasiveness of this technique is intriguing for VATS procedures and can be considered as a second choice whenever the TPVB is not feasible.

f. Erector spinae plane block (ESPB)

The ESPB is a newly described technique for providing thoracic anesthesia [60]. Under ultrasound guidance, about 20 mL of local anesthetic are injected 3 cm beside the interspinous line at T5 level deep to the trapezius, rhomboid and erector spinae muscles. ESPB has been proposed for thoracic neuropathic pain, rib fractures and as rescue in thoracotomy after epidural failure.

g. Chronic pain after thoracic surgery.

Recognising the clinical burden of chronic pain and its importance to patients, clinicians and providers, the James Lind Alliance has identified chronic pain after surgery as one of the top 10 research priorities in the surgical setting. Chronic pain following thoracic surgery may affect up to 80% of patients and it also remains an important problem after VATS procedures [61]. Intraoperative ketamine has not demonstrated protective effects and there is no conclusive data in regard to gabapentinoids for the prevention of chronic postsurgical pain. Currently the TOPIC2 investigators are conducting a pragmatic, large (over 1000 patients) multicenter randomized controlled trial in the UK towards authoritative evidence on the clinical and cost-effectiveness of

thoracic epidural versus paravertebral blockade in chronic post-thoracotomy pain [62]. The core tenet of the clinical trial is that these two analgesic treatment arms influence differently the principle mechanisms of pain triggering, processing and perception in the perioperative period affecting the development of more persistent chronic pain.

Conclusion

Thoracic anesthesia has developed tremendously over the last decades to match the major advances in surgical practice. Beyond technological advances in our toolbox and monitoring, there are also major conceptual developments.

While anesthesia has long practiced ***personalized patient management*** by careful titration of inhalational or intravenous anesthetics and pain control, the current surgical evolution, the availability of a range of anesthetic modalities and postoperative pain control techniques allows us to fully tailor our anesthetic management to individual patient need on a truly personalized level. The current era of thoracic anesthesia, therefore, can be characterized as ***precision intraoperative medicine***. [63] However, the role of the anesthesiologist is not only focused on the intraoperative period but on a broader responsibility in the perioperative process and on a more direct delivery of a truly ***perioperative medicine approach***. The pillars of this modern anesthetic mission include a new level of multidisciplinary communication and involvement along the entire patient pathway. Preoperatively this should be focusing on ***risk evaluation, risk management and patient optimization*** and championing ***enhanced recovery and fast tracking*** in the postoperative period.

Despite such progress, there are major remaining opportunities to reduce postoperative complications and improve patient outcomes. Several intriguing paradigms have ben identified whereby we may improve cancer free survival, further reduce the injuries impact of mechanical ventilation especially during OLV and there is a major need to prevent peripheral and central pain sensitization, fundamental trigger mechanisms of chronic pain. There are major high quality multicenter clinical trials underway to provide answers for particular aspects of these issues. However, there is much to learn from large scale analysis of our variable actual practice through large scale observation studies. Therefore, thoracic anesthesia is active, vibrant and fit for purpose in the 21st century.

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Complications in Thoracic Surgery

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Key Points

1. Postoperative complications can be life-threatening.
2. They can have an early or late presentation.
3. Prevention is essential for reducing their incidence.
4. Most complications require medical management only while others necessitate surgical intervention.
5. A prompt recognition leads to better outcome.

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Introduction

Post-operative complications are challenges in thoracic surgery settings, and are associated with longer hospital stays, as well as worse morbidity and mortality rates. Complications can appear in the early or late post-operative periods, with most requiring medical management only, and the remaining necessitating surgical intervention.

Prevention is the recognized as being key to reducing the incidence of postoperative complications and therein, every effort should be made to recognize and correct any preoperative risk factor. Below, we describe both the clinical signs and recommended management strategies for the most frequent early and late post-operative complications (Table 1a, b).

Early Complications

(1) Bleeding

The overall incidence of postoperative bleeding after lung resection has been reported to be between 1.3 and 3% [1, 2] and associated with 52% of chest re-explorations. Other causes have been attributed to the presence of bronchopleural fistulas (BPF, 17.9%), prolonged air leaks (PAL) (10.9%) and miscellaneous (19.3%) [3]. Currently, according to international guidelines, a major bleeding is defined as a blood loss

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Table 1 (a) Early postoperative complications after thoracic surgery. (b) Late postoperative complications after thoracic surgery

(a) Early complications
Bleeding
Cardiac complications
Arrhythmias
Early bronchopleural fistula
Pulmonary complications
Sputum retention, Pneumonia, Atelectasis
Pulmonary edema
Pleural complications
Empyema
Chylothorax
Nerve Injury
Phrenic nerve
Recurrent laryngeal nerve
(b) Late complications
Complications following thoracic incisions
Late postpneumonectomy bronchopleural fistula
Late bronchopleural fistula associated with a residual pleural cavity
Prolonged air leak without residual cavity
Pleural cavities without air leak
Right-to-left shunt
Postpneumonectomy syndrome
Lobar torsion and gangrene

greater than 200 mL/h. Major bleedings more than often result from inadequate hemostasis of either a bronchial artery or a chest wall vessel. Less frequently, these can be due to a ligature slippage of a major pulmonary vessel. The clinical signs of acute hypovolemia are often detectable and include hypotension, tachycardia, paleness and tachypnea; worsening bleeding is associated with a deterioration of these clinical signs. Along with the assessment of vital signs, measuring the amount of the blood in the collection chamber is the first and most important step leading up to diagnosis. Further confirmation can be obtained by chest X-ray, thoracic ultrasound or computed tomography (CT) scan; the latter being able to reveal even the sources of bleeding. In cases of bleeding from an intercostal or bronchial artery, as long as the patient is deemed stable, a mini-invasive procedure with percutaneous embolization is advisable [4]. However, in cases of severe bleeding or patient unsuitability, surgery is recommended [4].

(2) **Cardiac complications**

Worldwide, more than 10 million non-cardiac surgery patients annually experience significant myocardial injury within 30 days of surgery [5]. Regarding thoracic procedures, early postoperative cardiac complications are reported to be the second cause of perioperative morbidity and mortality [5]. The early postoperative period may also be complicated by the onset of myocardial infarction (MI) or cardiac ischemia, with reported incidence rates of 1.2% and 3.8%, respectively [5]. While herniation and tamponade can occur after procedures involving an opening of the pericardial sac, many studies have sought to identify new predictors of cardiac complications after thoracic surgery. Specifically, Rodseth et al. have suggested that an increased post-operative natriuretic peptide (NP) may be the most reliable independent predictor of cardiac mortality, nonfatal MI, and cardiac failure at 30 and 180 days after non-cardiac surgery [6, 7].

a.**Arrhythmias**

Atrial tachyarrhythmias, particularly atrial fibrillation (AF), are the most common cardiac complications following thoracic surgery, and are associated with increased morbidity and mortality, extended hospital stays and higher costs [8]. Following major resection using video-assisted thoracic surgery (VATS) the overall incidence rate of atrial tachyarrhythmias has been reported to be between 4 and 12%. Whereas, following the open approach, this rate has been reported to be between 12 and 30% [8]. AF is generally verified within 3 days of surgery and tends to resolve within seven days after the intervention. Possible risk factors for AF include: age > 70 years, male sex, pre-existing history of cardiac or valvular diseases, peripheral vascular disease, intrapericardial dissection, extent of pulmonary resection, intraoperative blood transfusions, postoperative electrolyte imbalance and hypoxia [9–12].

Recently, a prospective study has suggested that postoperative B-type NP (BNP) measurement might be an independent predictor of postoperative cardiopulmonary adverse events. Specifically, a BNP measurement of ≥118.5 pg/ml was associated with a 3-fold risk of developing cardiopulmonary complications [13]. Furthermore, it has been suggested that the presence of an asymptomatic patent foramen ovale (PFO) at baseline, might be predictive of postoperative AF in patients who had recently undergone major pulmonary resections for lung cancer [14]. Symptoms of atrial tachyarrhythmias can include palpitations, a sensation of a racing, uncomfortable irregular heartbeat, weakness, fatigue, light-headedness, dizziness, confusion, shortness of breath. Recommended treatment strategies include the administration of anti-arrithymics and the correction of any hydroelectrolytic imbalance.

(3) **Early bronchopleural fistula**

BPF is the communication between a bronchus and the pleural space, which can arise from bronchial dehiscence after either anatomic lung resection or bronchoplastic procedures. Its incidence has been associated with: segmentectomies (0.1%), lobectomies (0.2–3%), pneumonectomies (0.9–6.8%) and completion pneumonectomies (10%) [15, 16]. BPF is classified according to its time of onset: early (<7 days), intermediate (7–30 days) and late (>30 days) [17, 18]. Predisposing factors for BPF include right pneumonectomy, the need for post-operative positive pressure ventilation [19], residual carcinoma at the bronchial margin [20], extensive lymph node dissection, neo-adjuvant chemo-radiotherapy and age over 70 years [21].

Early BPF is more commonly due to surgical technical problems, while late fistula is associated with factors including diabetes mellitus, malnutrition, pulmonary or pleural infections and recurrence of neoplastic disease.

Worsening BPF symptoms are correlated with increasing fistula size and the presence of empyema. In fact, small fistulas, (less than a few millimeters) may be asymptomatic or suspected whenever a persistent, brisk air-leak with an air-fluid level is present. While, larger ones are usually associated with fever, sputum, cough, an air-fluid level at chest X-ray and pleuritic pain in the case of empyema. Radiological and clinical signs have been suggested as being pathognomonic of BPF following pneumonectomy. These include, at chest X-ray, a plunge in the fluid level of the residual pleural cavity associated with subcutaneous emphysema, fever with purulent sputum and/or a shift in the mediastinum contralateral [22]. CT scan is best able to reveal radiological signs of BPF, while the presence of BPF must be confirmed via bronchoscopy [22].

BPFs with diameters less than 8 mm can be successfully treated with bronchoscopy, while larger ones are not suitable for conservative management [23]. In the latter case, treatment options can include chronic open drainage, direct stump closure with intercostal muscle reinforcement, omental flap, trans-sternal bronchial closure, and thoracoplasty with or without extrathoracic chest wall muscle transposition [24].

Regarding post-pneumonectomy BPFs, drainage alone is recommended for patients in poor general condition with empyema.

Whereas, open window thoracostomy (OWT) is often considered to be a better option, as it allows for the cleansing of the pleural cavity. For patients in good general condition with early BPF (<30 days), re-closure should be considered [25].

(4) **Pulmonary complications**

a. **Sputum retention, pneumonia and atelectasis**

Sputum retention is the failure to clear secretions from the bronchial tree. It is known to be associated with the onsets of atelectasis, pneumonia, systemic sepsis, hypoxia and/or respiratory failure, leading to increased rates of morbidity and mortality. Sputum retention and mild atelectasis are best treated with physical therapy and bronchofiberoptic aspiration.

Minitracheostomy has been associated to significant reductions in the incidences of atelectasis and sputum related complications, especially in high risk thoracic patients [26].

Pulmonary morbidity is the most frequent complication following VATS lobectomy: around 3%, according to the Society of Thoracic Surgeons database. Risk factors include advancing age, preexisting pulmonary dysfunction, poor performance status, an open transthoracic approach, inadequate nutritional status, preoperative tobacco use, induction therapy and/or previous head and neck surgery due to its increased risk of aspiration pneumonia [27–31].

b. **Pulmonary edema**

Systemic inflammatory reaction after major surgical procedures generates changes in haemodynamic, endocrine and immune functions, able to modify hydrostatic pressure and pulmonary capillary permeability, leading to a generalized fluid retention [32]. Extra-vascular lung water (EVLW) is all the fluid within the lung outside the vascular compartment, and its presence is responsible for the development of pulmonary edema [33, 34]. Following thoracic surgery, several conditions are known to enhance EVLW expansion, such as thoracotomy, a rise in the permeability of the alveolar capillary membranes due to inflammatory states [35, 36], rapid fluid infusion, a decrease in the vascular bed due to a loss of pulmonary tissue, the manipulation of the lung and an increase in the capillary surface due to capillary recruitment. Likewise, EVLW expansion can trigger impairments in gas diffusion, therein facilitating the onset of postoperative acute lung injury, which is often associated with an increased risk of mortality, ranging from 20 to 100% [33].

Transpulmonary thermal indicator technique (PiCCO; PULSION Medical Systems, Munich, Germany) is currently considered the gold standard for the detection of EVLW expansion. However, it is an invasive, expensive and cumbersome procedure. Recently, lung ultrasonography has been proposed as a non-invasive alternative, suggesting that at 24-hour post lung resection, a significant B-line increase is significantly associated with BNP augmentation and an inversely correlated with the PaO_2/FiO_2 respiratory ratio [37].

(5) **Pleural complications**

a. **Empyema**

According to the Center for Disease Control, post-operative empyema is a surgical site infection (SSI) involving a preexisting space [38]. The reported rate of empyema, after lung resection, is between 0.3 and 4.7% [39–41]. Known risk factors for SSI include male sex [42], the presence of chronic obstructive pulmonary disease, major pulmonary resection [40], diabetes, steroid therapy and/or induction chemo/radiotherapy [41]. The diagnosis and management strategies for empyema are described in a dedicated chapter.

b. **Chylothorax**

Chylothorax is an accumulation in the chest cavity of a milky fluid containing lymphocytes, immunoglobulins, enzymes and fat (fat-soluble vitamins, chylomicrons, and triglycerides) [43]. The thoracic duct originates in the cisterna chyli and ascends posterior to the esophagus between the aorta and the azygos vein. The duct receives tributaries from

the bronchomediastinal trunk before exiting the mediastinum. Once the duct enters the neck, it […] terminates […] in the posterior confluence of the left jugular and subclavian veins. Chylothorax may originate from a tear of the thoracic duct or one of its collectors. The incidence after lung resections has been reported to be between 0.42 and 2.4% [44] and generally appears within 3 days post-surgery. Chylothorax after thoracic surgery and heart-lung transplantation have been reported to occur 7–82 days following surgery [45]. Its diagnosis can be reliably reached in the presence of a fluid concentration of triglycerides higher than that of plasma: triglyceride levels higher than 110 mg/dL and/or a fluid containing chylomicrons [43]. An appropriate management of chylothorax needs to consider the injury level, as well as the amount and duration of the chyle loss. Total parenteral nutrition or a diet without tryglicerides can often significantly reduce this loss. Here, somatostatin is recommended for its ability to inhibit gastrointestinal secretions [46]. As well, etilefrine, has been reported to trigger smooth muscle contractions, thus leading to reductions in the main lymphatic vessel diameters [47]. In cases of limited benefits from conservative management, surgical treatment with thoracic duct ligation is advisable. The identification of the thoracic duct can be achieved through a preoperative administration of a high intake of fat, preferably stained with methylene blue or Sudan black [48].

(6) **Nerve injury**

Nerve injury is reported in about 1% of patients undergoing thoracic surgery, as a result of direct surgical trauma, or indirect trauma due to retraction of adjacent structures [49].

a. **Injury to the phrenic nerve**

Phrenic nerve injuries cause diaphragm muscle dysfunction with respiratory impairment. In fact, because of its length it can be injured in the cervical area or in the thorax. Post-operative lesions can occur either after an open or VATS procedure during thymectomy, mediastinal lymph node dissection, or intrapericardial pneumonectomy. A postoperative chest X-ray, evidencing an elevation of the hemi diaphragm, can suggest phrenic nerve injury. Moreover, in cases of severe dyspnea, surgical treatment with diaphragmatic plication is recommended [49].

b. **Injury to the recurrent laryngeal nerve**

The two recurrent laryngeal nerves (RLNs) arise from the vagus nerves. The right one originates at the level of the subclavian artery, while the left one originates at the level of the aortic arch. Both nerves curve below and behind these arteries and proceed upward toward the larynx, providing motor innervation to the intrinsic laryngeal muscles, necessary for vocalization, swallowing and breathing. Injuries to RLNs can cause the inhalation of food, saliva, liquids, and/or vomit, and these can lead to the onset of pneumonia [50]. Left-sided RLN lesions can occur during the resections of centrally located lung tumours, or during mediastinal lymphadenectomy. Predisposing factors include induction chemotherapy, use of electrocautery and extended lymphadenectomy. Conservative treatments include voice building exercises, while surgical treatments include medialization laryngoplasty [49].

Late Complications

(1) **Complications following thoracic incisions**

The VATS procedures are associated with lower SSI incidences, compared to thoracotomy. The infection rate of the median sternotomy has been reported to range from 0.4 to 6.9%, while the mortality rate can vary between 7 and 80%. Preoperative risk factors for wound infections include diabetes mellitus, obesity, chronic obstructive pulmonary disease, irradiation, immunosuppression, malnutrition, renal failure, timing of antibiotic administration, intraoperative contamination, use of foreign bodies (bone wax), prolonged operative time and/or wound re-exploration [41, 51]. Superficial wound infections (skin and subcutaneous tissue) may be managed by local medicating and antibiotics.

While deep wound infections can lead to mediastinitis, which is a life-threatening condition, requiring prolonged open wound care and even sternectomy and reconstruction with viable and healthy tissue, such as muscle-cutaneous flaps or omental flap transposition [52, 53].

(2) **Late postpneumonectomy bronchopleural fistula**

BPFs are defined as late whenever onset is more than 30 days post-surgery. The reported overall incidence rate has been estimated to be between 0.9 and 6.8%. Onset is often associated with diabetes, malnutrition, infections and/or the recurrence of a neoplastic disease. BPF is present in up to 90% of patients with postpneumonectomy empyema. Currently recommended treatment includes pleural drainage, the resolution of the chest cavity infection, as well as the closure of the fistula and the obliteration of pleural cavity. Drainage has been described as a suitable option for empyema patients in poor general condition [54]. Patients with empyema and small BPFs can also be safely treated with minimally invasive strategies, such as VATS debridment of the pleural cavity, chest drainage and serial irrigation [55]. The most frequent technique for obtaining a sterile pleural cavity is through serial packing of the chest cavity with antimicrobial/antibiotic-soaked gauze, utilizing an OWT as originally described by Clagett and Geraci. This needs to be performed until tissue cultures become negatives or a visually healthy cavity with granulation tissues is obtained [56].

The most reliable techniques for closing BPFs are OWT and thoracotomy. In both cases, bronchial defects can be either restapled or resutured and buttressed with healthy tissues [57, 58]. Whenever a BPF cannot be managed transpleurally, an alternative could be the trans-sternal approach. Here, the main bronchus is sutured in an area that is deemed to be infection free [59]. Once the fistula has healed and the pleural cavity thought to be sterile, the postpneumonectomy cavity should become smaller over time. Finally, the OWT can be closed in multiple layers, with or without filling the cavity with an antimicrobial solution [60]. Only in cases of a persistent and relatively large pleural space, a tailored thoracoplasty may be advocated to obliterate the space with suitable tissue.

(3) **Late bronchopleural fistula associated with a residual pleural cavity**

A post-operative residual pleural cavity is an air-filled space that persists after lung resections. It is often associated with bilobectomy and upper lobectomy, especially whenever wedge resections or segmentectomies are concomitantly performed. This type of fistula is usually characterized by a benign evolution: the space tends to slowly fill with the remaining lung parenchyma or with a sterile fluid [61].

In cases of PAL, BPF should be ruled out and the pleural cavity be adequately drained. However, BPF after partial lung resections, with no pleural space left, usually spontaneously closes within a short time. Whereas, with large fistulas, closure should be attempted once the pleural cavity has been properly debrided and cleaned. Moreover, pneumoperitoneum has also been described for both the obliteration of the chest pleural cavity and the concomitant closure of the BPF [62].

(4) **Prolonged air leak without residual cavity**

PAL is a leak that lasts more than 5 days post-surgery, and in most cases it will spontaneously close within 2–3 weeks [63]. The incidences of PAL after lobectomy and segmentectomy have been reported to be 8.9% and 6.4%, respectively. The European Society of Thoracic Surgeons has developed a risk score to stratify the risk of a PAL following VATS lobectomy [64]. This score is composed of three variables: male gender (1 point), forced expiratory volume in one second <80% (1 point), body mass index <18.5 kg/m^2 (2 points). For class A (0 points), class B (1 point), class C (2 points) and class D (>2 points) the risk PAL is increased by 6.3%, 10%, 13% and 25%, respectively [65]. Whenever PAL is lower than a grade 4, according to the Cerfolio classification, patients can be discharged with a Heimlich valve [66]. Other suggested options for resolving PAL, whenever no pleural cavity is present, include pleurodesis with either chemical

agents or autologous blood and/or the use of endobronchial valves [67].

(5) **Pleural cavities without air leak**

A residual pleural cavity is frequent after lung resections and it usually spontaneously resolves over time, as a result of hyperinflation of the remaining lung, diaphragm elevation, mediastinal shift and intercostal space narrowing [68]. Many interventions have been described to reduce the pleural cavity, such as pleural tenting, pneumoperitoneum, as well as permanent transient techniques to induce phrenic nerve paralysis [69].

(6) **Right-to-left shunt**

PFO is a remnant of the fetal circulation, present in up to 25% of the general population and is considered an irrelevant condition in healthy subjects [70]. After thoracic surgery, interatrial shunting through PFO, can provoke a rarely observed complication known as platypnea-orthodeoxia which is characterized by dyspnea (platypnea) and hypoxia (orthodeoxia) assuming an upright posture which resolves by recumbency [71]. However, it is known to be more frequent after right pneumonectomy and can have an early or late presentation [72]. Regarding its pathophysiology, the following risk factors have been implicated: (1) the reduction of the pulmonary vascular bed which should lead to an increase in pulmonary vascular resistance [73], (2) the decrease in right ventricular compliance that could be exacerbated by perioperative fluid loading [74], (3) the postoperative modification of the mediastinic anatomy leading to an interatrial septum distortion (allowing the PFO to preferentially receive inferior vena cava flow) [71], (4) the relaxation and elevation of the right hemi-diaphragm, and finally, (5) the increased right-side pressures. Recently, it has been suggested that the presence of an asymptomatic PFO at baseline is associated with a three-fold greater risk of developing postoperative AF [14]. Moreover, in the same study, 11% of the patients with negative PFO at baseline, resulted positive following pulmonary resection. The Authors concluded that major pulmonary resection could have provoked the observed PFO [14].

(7) **Postpneumonectomy syndrome**

Postpneumonectomy syndrome is characterized by airway obstruction caused by the rotation of the mediastinum into the pneumonectomy cavity, usually occurring after a right pneumonectomy. When the syndrome occurs after a left pneumonectomy, it provokes a mediastinal shift into the left pleural space with a clockwise rotation of the mediastinum. Specifically, the trachea is pulled to the left and the right main bronchus is compressed by the vertebral column and/or the aorta. Currently, available treatment options include bronchial stenting, mediastinal repositioning with saline filled prostheses or aortic division with by-pass surgery accompanied with mediastinal repositioning [75, 76].

(8) **Lobar torsion and gangrene**

Lobar torsion and gangrene are rare postoperative complications due to the rotation of the broncho-vascular pedicle (generally 180 degrees) with subsequent obstruction of the airflow and vascular compromise. Predisposing conditions that favor lobar torsion include a mobile middle lobe along with complete interlobar fissures, a long hilar pedicle, or the presence of either pneumothorax or pleural effusion [77, 78]. Torsions more frequently involve the middle lobe after an upper lobectomy (70%); likewise, bilateral lobar torsions have also been described. Patient symptoms can include dyspnea, chest pain and respiratory distress with acidosis. Widely recognized symptoms of the resultant infarction include shock, sepsis and deterioration and tend to be rapidly progressing [79].

Lobar torsion can be suspected, when in the first postoperative days, a large pulmonary opacity is observed on chest X-ray. Whereas, bronchoscopy may show a narrow bronchial orifice and a distorted bronchial anatomy. CT can reliably confirm these findings, as it is able to detect a tapered obliteration of the proximal pulmonary artery and its accompanying bronchus and amorphous soft-tissue reduction at the site of the hilum [80, 81].

Once the diagnosis of lobar torsion is reached, surgical re-exploration is mandatory. If the lung is still viable, it can be preserved after its detorsion and stabilization; however, the risk of a secondary embolism remains. Whenever, the parenchyma evidences signs of hemorrhagic infarction, lobar resection or completion pneumonectomy is recommended [82]. Mortality rates can be extremely high whenever the torsion goes unrecognized or when surgical fixation or excision of the involved lobe is delayed.

Self-study

1. Which statement is true:
   (a) Early BPF is more commonly associated with factors including diabetes mellitus, malnutrition, pulmonary or pleural infections and recurrence of neoplastic disease.
   (b) Late BPF is more commonly due to surgical technical problems.
   (c) OWT is always necessary to properly manage BPF.
   (d) Recommended treatment for BPF includes pleural drainage, the resolution of the chest cavity infection, as well as the closure of the fistula and the obliteration of pleural cavity.

2. Which statement is true:
   (a) The incidence of PAL after segmentectomy is higher than after lobectomy.
   (b) PAL is the first cause of chest re-explorations.
   (c) PAL is a leak that lasts more than 5 days post-surgery, and in most cases it will spontaneously close within 2–3 weeks.
   (d) PAL is always associated with BPF.

Answers

1. Which statement is true:
   (a) Early BPF is more commonly due to surgical technical problems.
   (b) Late BPF is more commonly associated with factors including diabetes mellitus, malnutrition, pulmonary or pleural infections and recurrence of neoplastic disease.
   (c) OWT is often considered to be an option for the cleansing of the pleural cavity.
   (d) Recommended treatment for BPF includes pleural drainage, the resolution of the chest cavity infection, as well as the closure of the fistula and the obliteration of pleural cavity—**CORRECT**.

2. Which statement is true:
   (a) The incidence of PAL after lobectomy is higher than after segmentectomy.
   (b) PAL is the third cause of chest re-explorations. Postoperative bleeding after lung resection has been associated with 52% of chest re-explorations. Other causes have been attributed to the presence of BPF (17.9%), PAL (10.9%) and miscellaneous (19.3%).
   (c) PAL is a leak that lasts more than 5 days post-surgery, and in most cases it will spontaneously close within 2–3 weeks—**CORRECT**.
   (d) PAL can also be caused by a BPF.

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Pain Management for the Thoracic Surgical Patient

Atakan Erkılınç and Mustafa Emre Gürcü

Key Points

- Postoperative pain occurs as a result of inflammatory cell release triggered by surgical incision.
- Since post-thoracotomy pain occurs through different mechanisms, its management is more difficult.
- Multimodal analgesia is highly effective in pain control after thoracic surgery.
- Preemptive analgesia is a method that reduces acute postoperative pain by applying analgesia before tissue damage occurs.

Introduction

According to the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. The perception of pain includes a number of complex neurophysiological steps such as transduction, transmission, modulation and perception. Modulation of nociception may occur at any point such as peripheral, spinal, supraspinal, cognitive and neuroplasticity [1]. Despite the better understanding of pain pathophysiology and improvements in drug and drug administration methods, postoperative pain still remains as an important problem.

Postoperative pain is a process that starts with tissue damage caused by surgical incision and covers tissue healing period postoperatively. Surgical intervention leads to tissue damage and as a result, histamine and inflammatory mediators are released (bradykinin, prostaglandin, serotonin, etc.). The release of inflammatory mediators activates peripheral nociceptors and transduction and transmission of nociceptive information to the central nervous system begins. Stimuli delivered to the central nervous system through transmission cause suprasegmental and cortical responses, resulting pain perception [2]. Many systems have a role in this process such as neuroendocrine functions, respiratory and renal functions, gastrointestinal activity, circulatory and autonomic nervous system activity changes [3]. Postoperative pain is defined as a complication of surgery and inadequate analgesia which can lead to physiological and psychological problems.

Adequate treatment of pain is intended to minimize the amount and side effects of analgesic agents used for pain, thereby facilitating patient recovery and shortening hospital stay [4]. Complications that may develop due to inadequate pain control are particularly prominent

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in smokers, obese, elderly patients, and patients with cardiovascular disease. Postoperative pain is more common especially in major surgical procedures such as abdominal and thoracic surgeries, and it leads to more serious problems.

Thoracic surgical procedures are performed by thoracotomy or thoracoscopic methods. The physiopathology of post-thoracotomy pain is very complex. Nociceptive receptors are stimulated by skin incision, separation and retraction of muscles, and sometimes by fracture of the ribs. In addition, the ligaments are stretched, the costochondral joints are dislocated, and the intercostal nerves are injured, and this causes more pain. The pleura is damaged by surgical stripping, chest drains and residual pleural blood, and thus, the resulting inflammatory response activates more nociceptors. Central transmission of these multiple nociceptive signals increases pain transmission and pain perception through central sensitization [5]. There are many different sensory afferents that transmit nociceptive stimuli after thoracotomy. These afferents originate from the incision site, chest drains, mediastinal pleura, central diaphragmatic pleura, and ipsilateral shoulder [6]. Stimuli originating from the chest wall, rib and peripheral diaphragmatic pleura are transmitted through the intercostal nerves, and stimuli from the pericardium and mediastinum are transmitted through the phrenic nerves. Sympathetic nerves may play a role in the transmission of pain from the lung and mediastinum[5]. It has also been suggested that stretching the brachial plexus and shoulder distraction may contribute to pain in some patients [7].

Post-thoracotomy pain without adequate treatment is very serious. Pain associated with surgical wounds increases more with breathing and ventilation. Inspiration compresses damaged structures and initiates reflex contraction of expiratory muscles. Expiration, which is often passive, becomes active. Functional residual capacity often falls below the closing capacity and the airways are closed. This situation results in atelectasis, shunting and hypoxemia. Deep inspiration is limited by pain, forced expiratory flow decreases, and effective coughing becomes impossible. Clearance of secretions in the airways is reduced [5]. In addition, mobilization is delayed in patients with inadequate pain control, and this causes disruption of tissue oxygenation, and serious complications such as deep vein thrombosis. Increased plasma catecholamine levels due to severe pain result in increased systemic vascular resistance, cardiac workload and myocardial oxygen consumption, leading to severe increase in morbidity and mortality, especially in patients with coronary artery disease [8]. Postoperative intense pain may pave the way for the development of pain syndrome after thoracotomy.

Factors affecting pain after thoracic surgery [5];

- Informing the patient sufficiently before surgery,
- Existing or possible opioid tolerance in the patient,
- Pre-emptive analgesia administration,
- Gender (female),
- Age (young),
- Psychological factors (anxiety, depression),
- Surgical technique.

Effective analgesia reverses all these changes and improves pulmonary function after thoracotomy. Following thoracic surgery, this situation becomes even more important and relieving pain with effective analgesia reduces the complication rate by accelerating the healing process. Thus, by preventing the negative effects of pain, the length of hospital stay can be shortened with the early mobilization of the patient [9]. Adequate pain control for thoracic surgery should try to reduce opioid use and prevent side effects while combining multimodal, enteral and parenteral analgesia with regional analgesia or local anesthesia techniques [10].

Multimodal analgesia according to ERAS guideline recommendations:

(i) Co-administration of various analgesic drugs with different mechanisms of action in the peripheral and/or central nervous system;
(ii) The use of regional anesthesia;

(iii) Avoidance of opioids as much as possible;
(iv) Transition to oral medications as soon as possible.

All of the methods above have been recommended by ERAS for post-thoracotomy pain treatment [11].

Post-toracotomy Pain Treatment Methods

Systemic Analgesics

Systemic analgesics (opioid or non-opioid) are the main alternatives of invasive techniques. Furthermore, systemic analgesics can be used for the maintenance of analgesia in addition to invasive techniques. Ideally, opioids administered initially by intravenous patient-controlled analgesia (IV-PCA) and by orally are the main components of systemic analgesic treatment for thoracic procedures [12].

Systemic Opioids: Opioid analgesics are exogenous molecules that bind to specific receptors and produce morphine-like effects [13]. Opioids have the effect of reducing supraspinal and spinal sensitization with μ receptors, they also have the effect of reducing both central and peripheral sensitization via peripheral opioid receptors [1]. Systemic opioids can be administered orally, intramuscularly, intravenously, subcutaneously, or transcutaneously. However, the most preferred methods are oral, intravenous and intramuscular routes. They can be used in addition to multimodal analgesic methods for the treatment of severe pain due to thoracotomy when adequate analgesia cannot be achieved. Nevertheless, parenteral administration of opioids may cause undesirable effects such as respiratory depression, nausea and vomiting, decreased bowel motility and increased sphincter tone [14]. When compared to IM opioids, IV-PCA systems have been reported to provide better analgesia [15]. Tramadol is a weak opioid receptor agonist with less side-effect profile when compared to other opioids and has been recommended in ERAS programs for moderate-to-severe pain before administrating strong opioids for analgesia [16]. In addition, studies have shown that acute exposure to opioids may lead to develop acute opioid tolerance [17]. Because of all these side effects, it has been recommended to use in combination with other analgesics in order to reduce opioid use.

Non-steroid Anti-inflammatory Drugs: Prostaglandins have an important role in the inflammatory pathway [18], and NSAIDs inhibit prostaglandin synthesis by reversibly inhibiting the cyclooxygenase enzyme, and show anti-inflammatory and analgesic impacts [19]. They have been proposed as the standard treatment for analgesia after thoracotomy [20]. They can reduce opioid consumption by more than 30% after thoracotomy, as well. They may cause gastrointestinal mucosal damage, bronchospasm, renal and platelet function disorders [21, 22]. Acetaminophen is an antipyretic and analgesic agent with weak cyclooxygenase inhibition properties. This drug, which can be administered orally or rectally up to 4 gr per day, is effective on shoulder pain and has lower toxicity than NSAIDs [23]. Unlike NSAIDs and COX-2 inhibitors, acetaminophen has fewer side effects at clinical doses and is considered safe for patients at risk for renal failure [24]. Due to the wide margins of safety, it is frequently used in pain control after thoracotomy [25].

Ketamine: It's an antagonist of N-methyl D-aspartate. It has postoperative analgesic effect. It can be used in addition to opioids for patient controlled analgesia (PCA). Ketamine used by PCA in combination with opioids has been reported to be very safe, and it also reduces side effects associated with opioids, and is also associated with low postoperative pain scores and high patient satisfaction [26, 27].

Gabapentin: It is an alkalized amino-butyric acid analogue and is effective in the treatment of neuropathic pain [28]. It shows its antinociceptor effect by binding to $\alpha_2\delta$ subunits of voltage-dependent calcium channels [29]. Preoperative use of gabapentin can reduce the occurrence of acute pain by preventing central sensitization. There are some evidences that gabapentin

reduces early postoperative pain scores and opioid consumption within the first 24 hours in patients exposed to various surgical procedures [30].

Dexmedetomidine: Dexmedetomidine is a potent selective α_2–agonist agent with sedative, analgesic and anxiolytic properties. In addition to the anxiolytic and sedative use in intensive care unit, it can be used with local anesthetics paravertebrally especially for postoperative pain control. It has been reported that the addition of 1 μg/kg of dexmedetomidine to bupivacaine increases analgesia quality and duration in patients applied thoracic paravertebral block and undergoing modified radical mastectomy [31]. Paravertebral administration of dexmedetomidine as an adjuvant therapy for local anesthesia leads to a reduction in intraoperative anesthetic requirements, postoperative analgesia and opioid requirements [32].

Local and Regional Nerve Blocks

Thoracic Epidural Nerve Block: In ERAS protocols, epidural analgesia has been proposed as an important part of intraoperative pain management and has become the gold standard technique for pain control after major thoracic surgeries [10]. The thoracic epidural space starts from the lower edge of the C7 vertebra and continues to the upper edge of the L1 vertebra. The epidural space opens into the paravertebral space through the intervertebral foramina. The epidural catheter is placed into the epidural area by a needle called the "Touhy needle" by using hanging drop or resistance loss technique from between the thoracic spinous protrusions and local anesthetics (LA) or opioids are spread to bilateral nerve roots from this region; thus, analgesia is provided. The thoracic intervertebral space suitable for thoracic surgical procedures is between T4 and T8 (Fig. 1). Through this method, local anesthetics or opioids are used alone or in combination and adequate analgesia can be achieved. Starting to administration of thoracic epidural analgesia in the preoperative period may reduce the development of possible postoperative acute pain with a more effective way [33]. It is also associated with better postoperative pulmonary functions, lower incidence of postoperative pulmonary complications, earlier return of bowel functions, shorter intensive care unit periods and shorter hospital stay. However, it has adverse effects on cardiac output, stroke volume, right ventricular contraction and urinary excretion [34]. Thoracic epidural analgesia using the combinations of local anesthetic and opioid is an important analgesic method for acute pain management in patients undergoing thoracic and upper abdominal surgery. It provides better postoperative analgesia compared to parenteral opioids, reduces pulmonary complications and mechanical ventilation time and contributes to faster postoperative recovery by reducing postoperative catabolism and postoperative ileus time after abdominal surgery. It also reduces morbidity and mortality in patients with multiple rib fractures [35]. Epidural analgesia used for patients undergoing major thoracic or abdominal surgery results in both statistically and clinically significant decrease in the risk of postoperative pneumonia. In addition, it improves pulmonary function and arterial oxygenation and reduces the risk of myocardial infarction [36]. It has been reported that thoracic epidural block in esophagus cancer surgery performed with open thoracotomy technique results in less postoperative pain, reduces stress response, hospital stay and treatment costs, and improves gastrointestinal system functions [37]. Thoracic epidural anesthesia has complications such as infection, epidural hematoma, nerve root injury, intravascular injection, subdural and subarachnoid injection and rarely respiratory depression. Therefore, epidural block requires preoperative sufficient time, good technique and experience [38].

Intercostal Nerve Block: Intercostal nerve block is widely used by many centers especially in thoracic surgery because of its easy application. There are 12 intercostal nerves that provide sensory innervation for the back, trunk and upper abdominal region, and muscular innervation for the intercostal muscles. Each intercostal nerve originates from the spinal cord roots at the

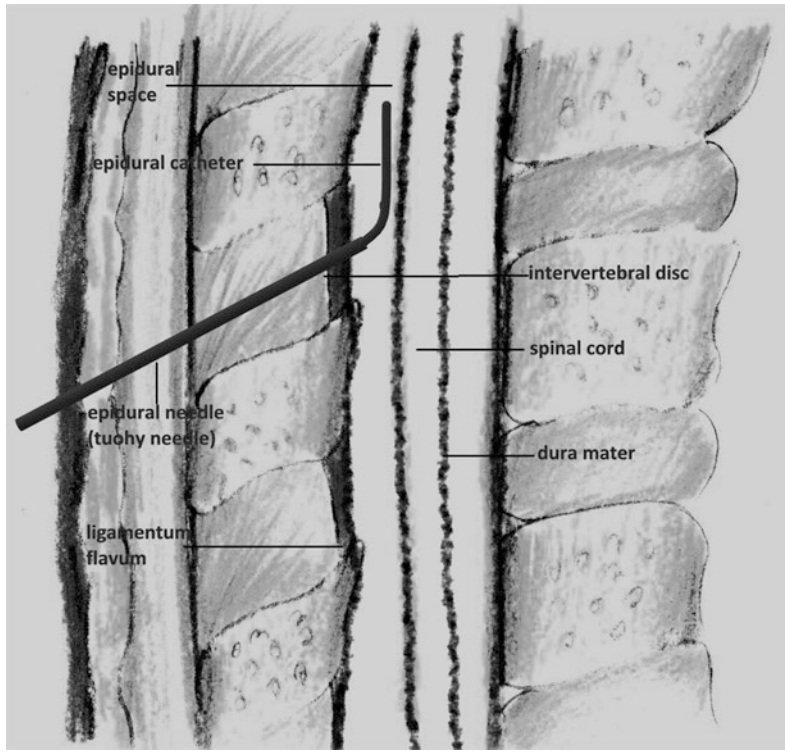

Fig. 1 Epidural space anatomy and epidural block

same vertebral level as the ribs with which it is located. Each spinal nerve is divided into dorsal and ventral branches as soon as it exits the spinal cord. The dorsal branch provides motor and sensory innervation of the paravertebral muscular system and sensory innervation of the skin and subcutaneous tissue. The ventral branch, on the other hand, continues anterolaterally and forms the intercostal nerve [39] (Fig. 2). Administration of intercostal block+intravenous patient-controlled analgesia provides pain control close to epidural analgesia and reduces opioid consumption in these patients [34]. Intercostal block administered in the first 24 hours postoperatively can provide sufficient pain control in the second postoperative day together with epidural catheter. The combination of both anesthetic techniques may provide an ideal pain management in patients undergoing thoracic surgery [40]. The risk of pneumothorax and the need for repeated doses due to its inability to provide long-term analgesia are the disadvantages of this method. Due to its proximity to vascular structures, local anesthetics pass rapidly into the systemic circulation and may cause systemic toxicity. It may also cause hypotension and respiratory failure. Therefore, one should be careful in the use of this anesthetic agent [3].

Paravertebral Nerve Block: Spinal nerves in the thoracic paravertebral space are blocked by local anesthetics in this method. The thoracic paravertebral space (TPVS) is a wedge-shaped potential space that lies on either side of the vertebral column. The anterior and lateral borders are formed by the parietal pleura, the posterior border is formed by the superior costotransverse ligament, and the medial border is formed by the posterolateral surface of the vertebral column, the intervertebral disc and the intervertebral foramen where the vertebral nerves arise [41]. The thoracic paravertebral nerves originate from the intervertebral foramen. They are divided into two main branches as posterior and anterior. The

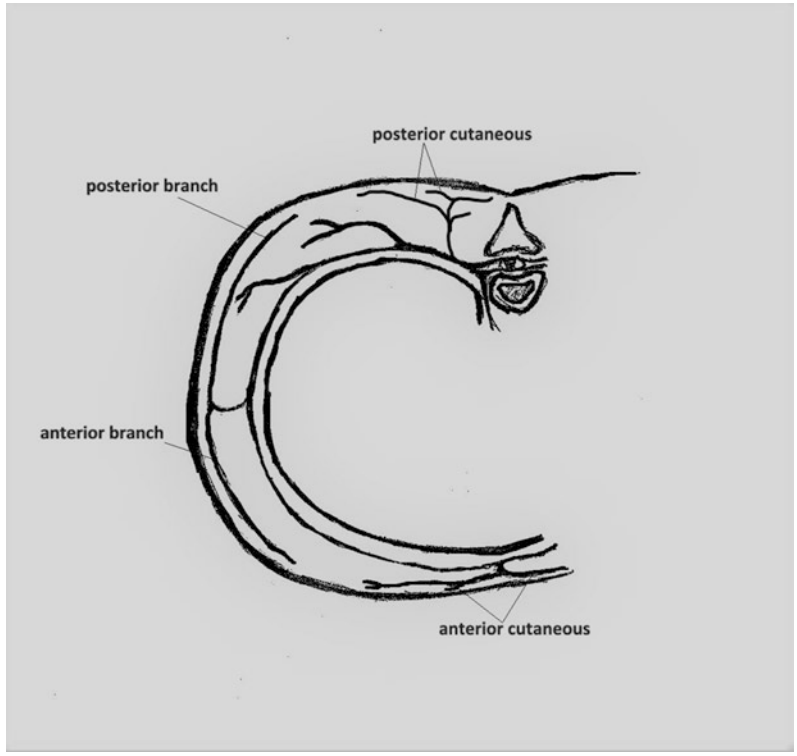

Fig. 2 Intercostal nerve anatomy

posterior branch innervates the facet joint, back muscles, and the skin in that region, while the anterior branch follows the subcostal groove and forms the intercostal nerves (Fig. 3). Intercostal and subcostal nerves innervate the peritoneum, skin, muscle, ribs and parietal pleura. As TPVS is closely adjacent to the epidural and intercostal space, local anesthesia application from a single injection site allows analgesia and anesthesia in many dermatomes [42]. Adequate analgesia can be achieved with thoracic paravertebral block in patients undergoing thoracotomy, cholecystectomy and nephrectomy [43]. The advantages of this method are that it does not cause respiratory depression and can be applied safely in patients with coagulopathy. It can be administered percutaneously or with open method. Local anesthetics administered by this method are spread over the paravertebral space over a long period of time. Therefore, this method should be supported with additional analgesic agents and techniques in order to ensure adequate analgesia in the early postoperative period. This method has complications such as pleural punction, pulmonary bleeding, dural punction, hypotension, nerve damage and central nervous system toxicity [5].

Intrathecal Opioid: Intrathecal opioid use for postoperative pain was first described in 1979 [44] and has become the preferred anesthetic technique for its easy administration (Fig. 4). Although it provides long-term postoperative analgesia, its use is limited compared to epidural analgesia due to the incidence of side effects (nausea, vomiting, pruritus, urinary retention and delayed respiratory depression) [45]. It has been reported that intrathecal sufentanil and morphine administration after thoracotomy reduced the need for IV morphine in the first 24 hours postoperatively, and that VAS and VRS scores associated with rest and cough were lower in the same period but there was no difference in IV morphine consumption and pain scores after 24 hours [46]. In another study, intrathecal

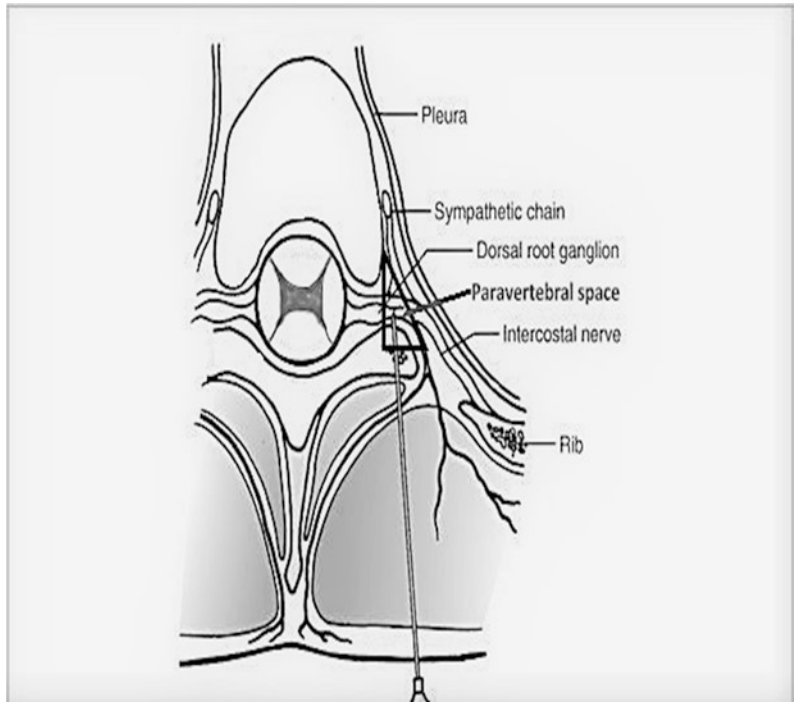

Fig. 3 Thoracic paravertebral space anatomy

morphine or combined sufentanil and morphine were found to reduce pain more both at rest and with cough compared to IV patient-controlled analgesia and reduced the need for IV morphine on the first postoperative day after posterolateral thoracotomy [47].

Interpleural Block: It is performed by injection of local anesthesia between parietal and visceral pleura in order to perform ipsilateral somatic block in more than one thoracic dermatome [48]. After thoracotomy, the volume of the intrapleural space expands and contains blood and air. The effects of surface tension forces reduce and the spread of local anesthetics is limited mainly by gravity. Dilution of the applied local anesthetic agents with intrapleural blood and the loss of injected local anesthetics via chest drains reduce the effectiveness of this technique more [5] (Table 1).

Pre-emptive Analgesia: The concept of pre-emptive analgesia was first introduced by Crile and means that analgesic treatment is performed before surgical incision or tissue damage [49]. Pre-emptive analgesia is based on relieving pain resulting from surgical intervention which leads to peripheral and central sensitivity. Peripheral sensitivity is the increase of pain as a result of the decrease of pain threshold in the terminal nerve endings caused by secretion of inflammatory mediators at the wound site. Central sensitivity, on the other hand, occurs when intense afferent impulses originating from the wound site increase the excitability of neurons in the dorsal horn of the spinal cord. Peripheral or central sensitivity results in increased sensitivity to pain clinically at the site of damage or inflammation [50]. Therefore, theoretically blocking surgical pain impulses should result in reduced pain signals and the timing of analgesic administration should also be important. This afferent blockade of nociception continues during the perioperative and postoperative periods [1]. Pre-emptive analgesia aims to reduce acute postoperative pain and prevent the development of chronic postoperative pain [10]. Pre-emptive analgesia can be defined as: (i) starts before

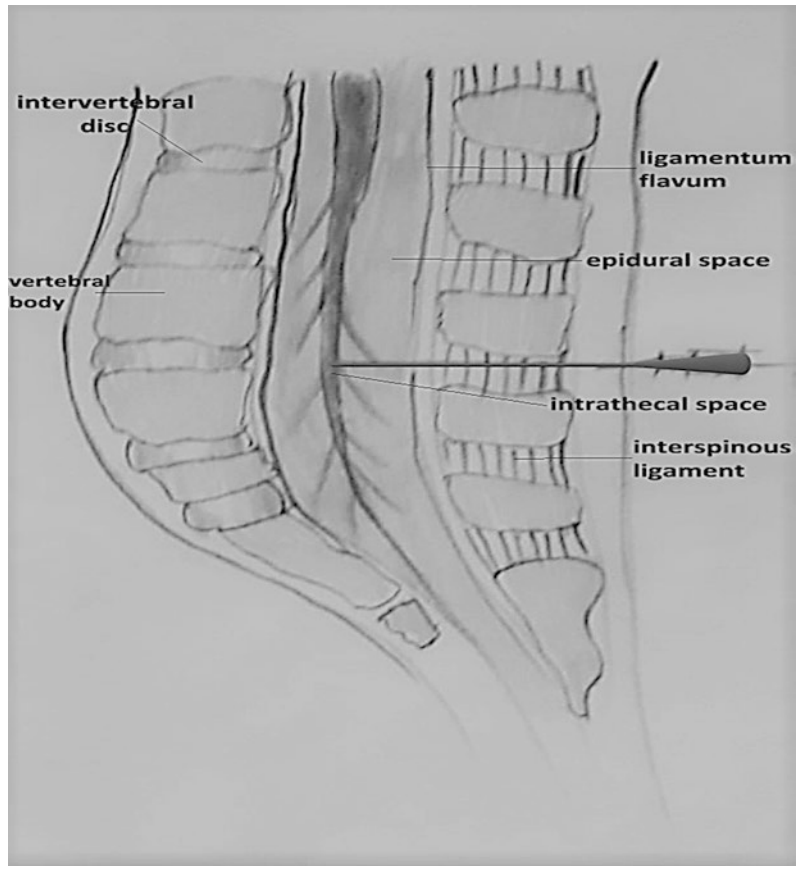

Fig. 4 Intrathecal anatomy and block

surgery (ii) prevents central sensitization due to incision injury (only covers operation time); and (iii) inhibits the development of central tenderness resulting from incisional and damaged injuries (includes operation time and the early postoperative period) [51]. Preoperatively initiated thoracic epidural analgesia has the most satisfactory results in controlling post thoracotomy pain during the acute and chronic period and has been shown to reduce the incidence of chronic pain compared with postoperative analgesia (epidural or IV) [52]. Although some studies have shown that the use of several analgesic techniques preoperatively reduces the need for analgesics and pain scores in the early postoperative period, this effect was not revealed as significant in most of the randomized clinical trials [53].

Cryoanalgesia: This is the process of freezing the peripheral nerves at −60 degree with liquid nitrogen. Cryoanalgesia is a simple and inexpensive method that does not cause long-term histological damage to the intercostal nerves and can be used for long-term pain control after thoracotomy [54]. Although intercostal nerve cryoanalgesia combined with small dose subcutaneous morphine can provide effective postoperative pain control, it has been reported that it causes neuropathic pain induced by cryoanalgesia for pain control after thoracotomy and increases the incidence of long-term pain according to some study results [55].

Transcutaneous Electrical Nerve Stimulation (TENS): Transcutaneous electrical nerve stimulation (TENS) has been used as an adjuvant treatment for chronic and acute pain

Table 1 Adult analgesic regimes for regional Analgesia (modified from Pennefather SH, McKevith J.) [5]

	Dose
Thoracic epidural blocks	
Levobupivacaine	%0.1
Ropivacaine with	%0.15
Fentanyl	4–5 μg mL^{-1}
Sufentanil	1 μg mL^{-1}
Hydromorphine	10–25 μg mL^{-1}
Intercostal nerve blocks	
Injection sites T3–T7	0.25% Levobupivacaine + epinephrine 1:200,000 3–5 mL per site
Paravertebrals blocks	
Lower dose regime	
Loading dose	0.3 mL kg^{-1} 0.25% Levobupivacaine
Maintenance	0.1 mL $kg^{-1}h^{-1}$ 0.25% Levobupivacaine
High dose regime	
Loading dose	20 mL 0.5% Levobupivacaine
Maintenance	0.1 mL kg^{-1} h^{-1} 0.5% Levobupivacaine
Intrathecal opioids	
	Morphine 200 μg + sufentanil 20 μg
	Morphine 500 μg + sufentanil 50 μg

Table 2 Summary and recommendations [10]

Technique	Recommendation level	Evidence level
Regional anesthesia	Strong	High
Combination of acetaminohen and NSAIDs	Strong	High
Ketamine	Strong	Moderate
Dexamethasone	Strong	Low

control in various medical and surgical conditions since the early 1970s [56]. It has been reported that opioid use is significantly less in TENS-treated patients than in the placebo group in the first 48 hours postoperatively, and it can be used safely in patients with liver and kidney disease since it has no side effects and is easily applicable [57]. In another study, it has been suggested that TENS usage for one hour per day on the second postoperative day reduced pain emerging at rest and with cough in patients receiving bupivacaine+fentanyl treatment after thoracotomy [58] (Table 2).

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The Neck Lymphnodes

Surgical Anatomy of the Neck

Adrian Schubert, Lluís Nisa, Hergen Friedrich, and Roland Giger

Key Points

- More than 300 lymph nodes are in the fatty-connective tissue of the neck between the muscular fasciae, carotid sheath and the visceral fascia of the neck
- Lymph nodes can be grouped anatomically or in levels defined by radiological/anatomical margins
- Nodal levels at risk of metastases can be predicted by the localization of the primary tumor as the lymph drainage follows sequential and constant ways

Introduction

Before performing a neck dissection, it is important to know well the cervical anatomy with emphasis on important structures and landmarks. The aim of this procedure is the dissection of the more than 300 lymph nodes harbored in the fatty-connective tissue of the neck, between the muscles and vital structures, particularly in patients with head and neck squamous cell carcinoma (HNSCC) of the mucosa and skin, with salivary gland and thyroid cancer, featuring known or suspected metastatic disease. The lymphatic drainage of the scalp and facial skin, the mucosa of the upper aerodigestive tract, and salivary and thyroid glands follows a specific pattern. The localization of metastatic lymph nodes are sequential in the drainage path of the primary tumor and are predictable with a high level of confidence.

Embryology

The neck is an anatomically rich region that contains vital and functionally important structures. Their anatomical location and some pathological behaviors are a direct result of the embryologic development. In humans, there are four pharyngeal arches and the structures rising from them are summarized in Table 1 [1].

Cervical Anatomy

Cervical Fasciae

Another basic system to consider dissecting the neck is its fascial system, which delineates the layers followed during the surgery.

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Table 1 Pharyngeal arches

Arch	Muscles	Nerves	Vessels	Skeletal derivates
Pharyngeal arch I	Muscles of mastication, mylohyoid, anterior digastric belly, tensor tympanic, tensor veli palatini	CN V trigeminal (mandibular nerve)	Maxillary artery	Malleus, incus, spheno-mandibular ligament
Pharyngeal arch II	Muscles of facial expression, stapedius, posterior digastric belly, stylohyoid	CN VII facial	Stapedia artery	Stapes, styloid process, stylohyoid ligament, part of hyoid
Pharyngeal arch III	Stylopharyngeus	CN IX glossopharyngeal	Internal carotid artery	Part of hyoid
Pharyngeal arch IV&VI	Cricothyroid, levator veli palatini, pharynx constrictors, intrinsic larynx muscles	CN X vagus (superior laryngeal nerve, recurrent laryngeal nerve)	Right subclavian artery, aorta	Laryngeal cartilage

CN cranial nerve

There are three muscle fasciae, a visceral fascia and the carotid sheath. The superficial fascia is subplatysmal, encases the whole neck and encircles the sternocleidomastoid muscles. Between the platysma and the superficial fascia lie the anterior and superficial jugular veins, as well as sensible nerves, most prominently the greater auricular nerve. The pretracheal fascia runs in front of the visceral fascia and encircles the infrahyoid muscles. The prevertebral fascia reflects the deep border of the neck. The carotid sheath and the visceral fascia separate the fatty-connective tissue from the vascular-nerve sheath and the organs of the neck (larynx, trachea, pharynx, esophagus, thyroid gland), respectively. Table 2 summarizes the fascial layers and their contents [1].

Lymphatic System

The lymphatic drainage of the scalp and facial skin, the mucosa of the upper aerodigestive tract, and salivary and thyroid gland follows a specific pattern. The fatty-connective tissue between the fascial layers of the neck contents more than 300 lymph nodes. Lymphatic vessels transport the interstitial fluid (lymph) back to the blood. Like other vessels and similar to veins, their walls consist of three layers (endothelium, smooth muscle, adventitia) and valves. Lymph nodes are filter stations in the lymphatic system and an important part of the adaptive immune system. Due to the rather consistent drainage patterns, the site of metastatic lymph nodes can be deduced from the location of the primary tumor. There is a variation in density of lymphatic vessels in different areas of the upper aerodigestive tract; therefore, the frequency of neck lymph node metastases depends not only on the size of the primary tumor, but also on its localization. The glottic region within the larynx for example has a poor supply of lymphatic vessels and nodal metastases occur almost exclusively in advanced stages [2]. In contrast, the supraglottic area contains much more supply of lymphatic vessels, and therefore, metastases occur even at early stage disease. Even for a single organ like the larynx, specific subsites follow substantially different patterns of lymphatic drainage, a phenomenon with profound implications when planning treatment strategies. The presence of metastasis correlates with a poorer outcome in all localizations [3].

Anatomical Lymph Node Groups

Lymph node groups can be described by their anatomical localization (e.g. jugulo-digastric lymph nodes). The preauricular, periparotid and intraparotid lymph nodes correspond to the scalp, frontal skin and upper part of the face. The retroauricular and suboccipital lymph nodes drain the posterior part of the scalp and posterior part of the ear. The mucosa of the upper aerodigestive tract drains to the lateral cervical lymph nodes. The submental group, the group anterior to the facial vessels and submandibular group are situated in the submental and submandibular triangle of the neck. The deep jugular lymph nodes are attached to the internal jugular vein and contain the jugulo-digastric, jugulo-omohyoid and subclavian group. The lymph nodes of the posterior triangle of the neck consist of the spinal group located around the accessory spinal nerve and transversal group

Table 2 Cervical fasciae

Cervical fasciae	Contents
Lamina superficialis	Encircles the entire neck around the trapezius and levator scapulae muscles, and also the sternocleidomastoid muscles
Lamina pretrachealis	Encircles the infrahyoid muscles
Lamina prevertebralis	Encircles the scalene, prevertebral and autochthonous back muscles
Carotid sheath	Encircles the neurovascular bundle (carotid artery, internal jugular vein, vagus nerve)
Lamina visceralis	Encircles larynx, trachea, pharynx, esophagus and thyroid gland

in the inferior part of the posterior triangle. The central compartment merges the delphian lymph node on the midline anterior to the larynx and the lymph nodes around the thyroid gland, draining these two organs. The tracheoesophageal lymph nodes are sequential to the thyroid gland, hypopharynx, cervical esophagus and subglottic larynx [4]. The lymph node groups by anatomical localization and area of drainage are summarized in Table 3.

Level System of Cervical Lymph Nodes

In the clinical setting, an international known level system (I–VI) rather than anatomical locations is preferentially used to describe the localization of the metastatic lymph nodes and the extension of the neck dissection [5]. In the following paragraphs, we describe in detail the characteristics of the different levels with their content regarding surgical procedures. Figure 1 gives an overview of the neck anatomy and Fig. 2 shows the outlines of the different lymph node groups.

Levels IA and IB, Submental and Submandibular Group

The boundaries of the level IA (submental group) are laterally the anterior belly of both digastric muscles, caudally the hyoid bone and deeply the muscles of the floor of mouth, especially the mylohyoid muscle. Level IA drains the ventral and medial aspects of the floor of mouth, the anterior tongue, the anterior mandibular alveolar ridge and lower lip. The level IB (submandibular group) contains lymph nodes within the boundaries of the anterior and posterior bellies of the digastric muscle, the stylohyoid muscle and the mandible. The *en block* resection of this level encloses the submandibular gland. The marginal mandibular branch of the facial nerve runs subplatysmal over the submandibular gland and is at risk. As a rule of thumb, the nerve stays above a virtual line two fingers below the lower ridge of the mandible bone. Therefore, skin incisions in the neck should avoid this area. Additionally, the facial artery and vein run next to the gland. The branch of the facial nerve goes over the vessels and can be saved by ligating the vessels and turn them up in direction to the face. The lingual nerve with the submandibular ganglion sits in the depth under the gland. It is mainly responsible for the sensible innervation of the anterior two third of the tongue. The hypoglossal nerve is found infero-medial of the gland typically under the digastric muscle as its landmark and innervates the muscles of the tongue. The nerve enters the tongue from caudal between the hyoglossal and mylohyoidal muscle. The lymph nodes of level IB might harbor metastasis from cancers of the anterior nasal cavity, oral cavity, skin and soft tissue structures of the midface and submandibular gland.

Levels IIA and IIB, Upper Jugular Group

Tissue from the level of the skull base to the inferior border of hyoid bone is defined as level II. The anterior/medial boundary is the

Table 3 Anatomical lymph node groups and area of drainage

Lymph node groups	Area of drainage
Preauricular, periparotid and intraparotid	Scalp, frontal skin and upper part of the face
Retroauricular and suboccipital	Posterior part of the scalp and posterior part of the ear
Submandibular and submental	Anterior nasal cavity, oral cavity, soft tissue structures of the midface, submandibular gland and lower lip
Jugulo-digastric, jugulo-omohyoid and subclavian	Almost all subsides of the mucosa, skin, salivary glands and thyroid gland
Posterior triangle	Nasopharynx, oropharynx and thyroid gland
Central compartment	Thyroid gland, larynx, piriform sinus and cervical esophagus

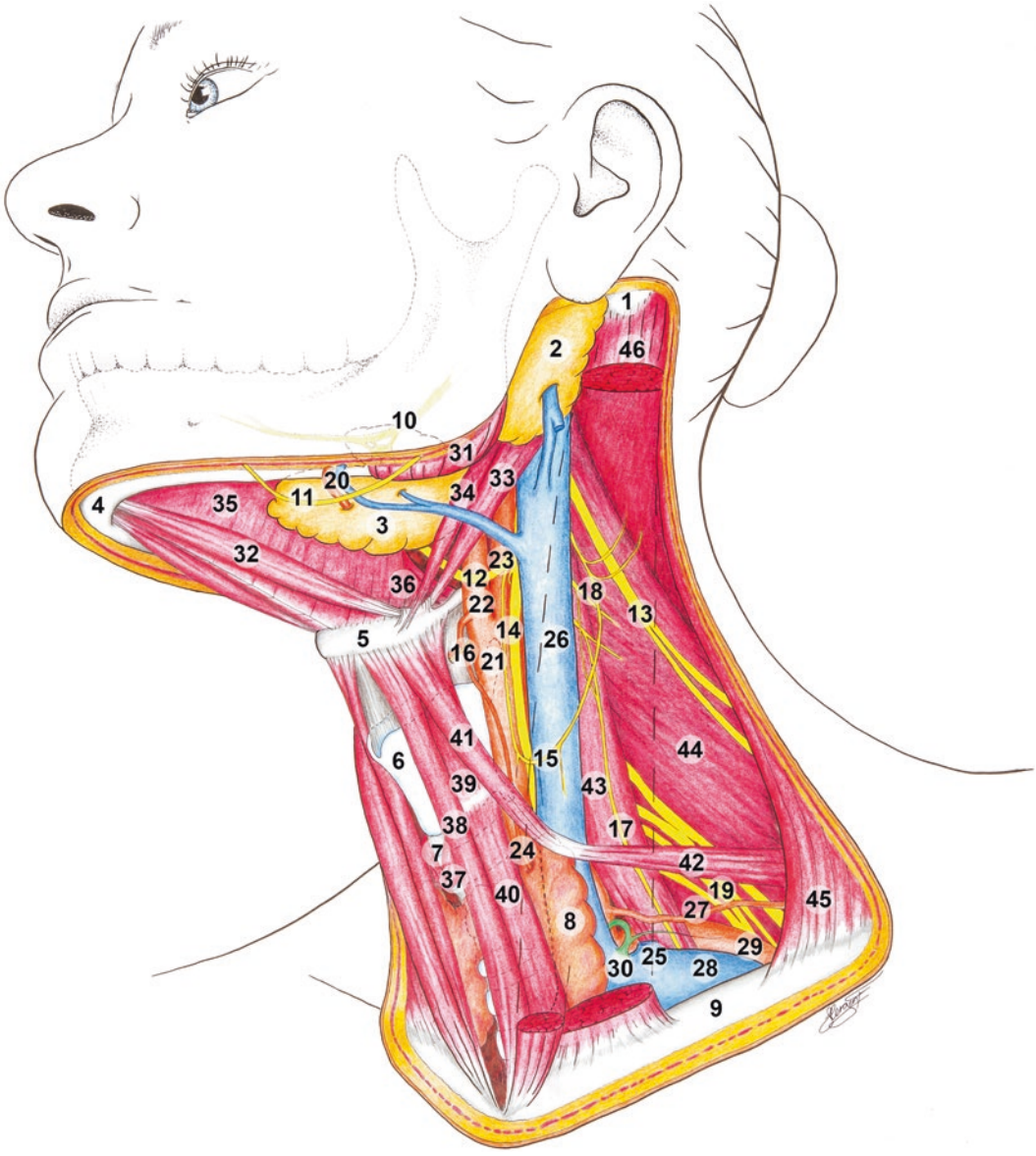

Fig. 1 Important anatomical structures of the neck (for better visibility sternocleidomastoid muscle and external jugular vein were cut cranially and caudally; the border of the sternocleidomastoid muscle is still shown as a broken line). **Glands, bones and cartilages** 1 Mastoid process; 2 Parotid gland; 3 Submandibular gland; 4 Mandible; 5 Hyoid bone; 6 Thyroid cartilage; 7 Cricoid cartilage; 8 Thyroid gland; 9 Clavicle. **Nerves** 10 Lingual nerve; 11 Marginal mandibular branch of the facial nerve; 12 Hypoglossal nerve; 13 Spinal accessory nerve; 14 Vagus nerve; 15 Ansa cervicalis; 16 Superior laryngeal nerve; 17 Phrenic nerve; 18 Cervical plexus; 19 Brachial plexus. **Vessels** 20 Facial vein and artery; 21 Common carotid artery; 22 External carotid artery; 23 Internal carotid artery; 24 Superior thyroid artery; 25 External jugular vein; 26 Internal jugular vein; 27 Transverse cervical artery; 28 Subclavian vein; 29 Subclavian artery; 30 Lymphatic thoracic duct. **Muscles** 31 Masseter muscle; 32 Anterior belly of digastric muscle; 33 Posterior belly of digastric muscle; 34 Stylohyoid muscle; 35 Mylohoid muscle; 36 Hyoglossus muscle; 37 Cricothyroid muscle; 38 Sternohyoid muscle; 39 Thyrohyoid muscle; 40 Sternothyroid muscle; 41 Superior belly of omohyoid muscle; 42 Inferior belly of omohyoid muscle; 43 Anterior scalene muscle; 44 Medial and posterior scalene muscles; 45 Trapezius muscle; 46 Sternocleidomastoid muscle

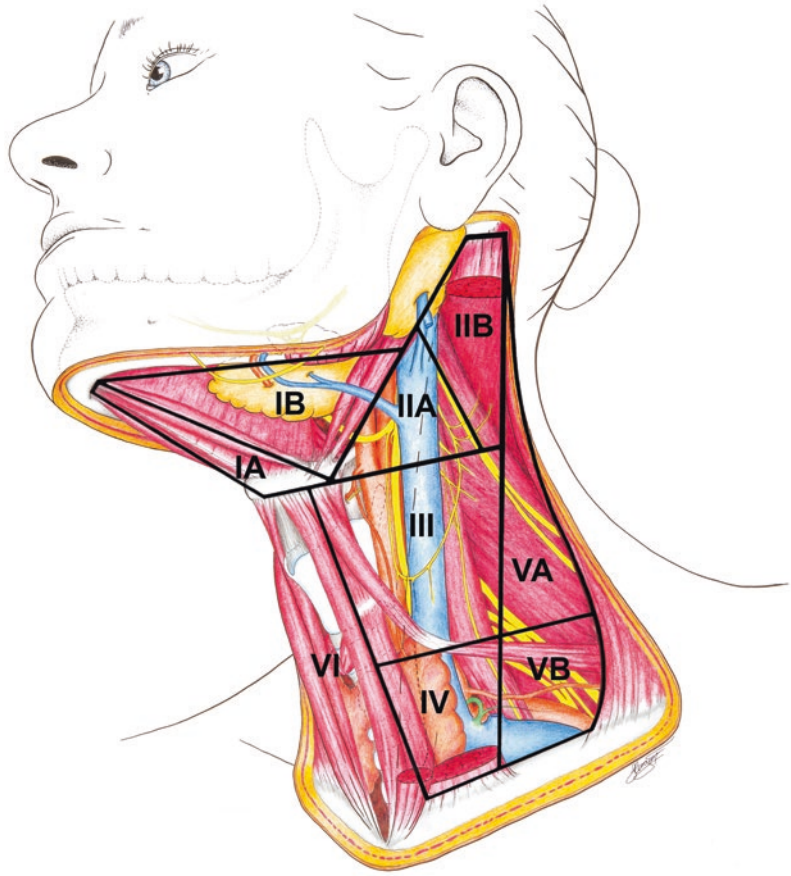

Fig. 2 The level system to describe the site of lymph nodes in the neck (no border is shown for Level VI; for this level the neck has to be seen from an anterior view and the lateral borders of level VI are the left and right carotid artery). **IA/IB** Submental/submandibular group; **IIA/IIB** Upper jugular group; **III** Middle jugular group; **IV** Lower jugular group; **VA/VB** Posterior triangle group; **VI** Anterior (central) compartment group

posterior belly of digastric muscle, the posterior/lateral boundary is the posterior border of the sternocleidomastoid muscle. The vertical plane is defined by the spinal accessory nerve, which runs from superior medial to inferior lateral through the sternocleidomastoid muscle and is found often surprisingly superficial. The spinal accessory nerve delimits anteriorly/medially sublevel IIA from IIB. The spinal accessory nerve innervates the sternocleidomastoid and trapezius muscles. In relation to the internal jugular vein, it has three variants crossing the vein. In the majority of cases, it crosses laterally/anterior of the vein, in the second variant the nerve runs behind the vein and in rare cases even through the vein. In most cases, the spinal accessory nerve divides as it passes through the sternocleidomastoid muscle. On the other hand, in rare cases there is a division before the nerve reaches the muscle [6]. Besides the spinal accessory nerve and the internal jugular vein, the vagus nerve and the carotid artery are situated in level II encircled by the carotid sheath. The common carotid artery divides at the bifurcation into the internal and external carotid artery. Important branches of the external carotid artery encountered during neck dissection are the facial and superior thyroid artery as they are often used to anastomose free flaps. The facial artery comes deep from the posterior belly of the

digastric muscle, and then passes the submandibular gland in a grove on the posterior border of the gland and winds around the inferior border of the mandible. In rare cases, the artery pierces the gland. The occipital artery is found posterior in level IIB. Metastasis from almost all subsides of the mucosa and the parotid gland can arise in level II. This is the reason why level II is removed in all modalities of neck dissections (see Chap. 6).

Level III, Middle Jugular Group

Level III extends from a horizontal plane through the hyoid bone to a horizontal plane through the inferior border of the cricoid cartilage. The anterior/medial border is the lateral border of the sternohyoid muscle and the posterior/lateral boundary is the posterior border of the sternocleidomastoid muscle. The plane formed by the cervical plexus also separates level III from level V in the depth. The neurovascular bundle (carotid artery, internal jugular vein, vagus nerve) crosses level III and the ansa cervicalis follows the internal jugular vein. The ansa cervicalis has a highly variable course along the internal jugular vein and attaches to the hypoglossal nerve without exchanging fibers. It innervates the infrahyoid muscles. Cancers arising from the oral cavity, nasopharynx, oropharynx, hypopharynx and larynx may metastasize into level III.

Level IV, Lower Jugular Group

This group contains lymph nodes from the lower third of the internal jugular vein from a horizontal plane through the inferior border of the cricoid cartilage to the clavicle. Anteriorly, it reaches the lateral border of the sternohyoid muscle; the posterior boundary is the posterior border of the sternocleidomastoid muscle. The neurovascular bundle crosses also this level vertically. The cervical circumflex vessels are crossing almost horizontally in the lower third of the level. At the lower boundary of level IV, the subclavian vein can be found as well as the lymphatic thoracic duct on the left side. The thoracic duct drains the lymph from the lower part of the body. It rises next to the spine through the chest, loops behind the internal jugular vein above the level of the subclavian vein before descending again and entering in the venous angle into the brachiocephalic vein together with the lymph vessels draining the left arm and left side of the head and neck. The right lymphatic duct drains from the right arm, right thorax and right side of the head and neck. In various combinations, it empties usually into the confluence of the right subclavian and internal jugular vein. During surgery, it is uncommon to see the right lymphatic duct and it causes less chyle leaks than the lymphatic thoracic duct on the left side. Metastasis from the hypopharynx, cervical esophagus and the larynx can arise in level IV, as well as from bronchial carcinomas. Metastases from a lung cancer in level IV (below the inferior border of the cricoid cartilage or the omohyoid muscle) are considered as regional lymph nodes metastases, corresponding to zone 1R and 1L in the TNM classification of pulmonary carcinomas. Metastatic lymph nodes above those borders are considered as distant metastatic disease.

Levels VA and VB, Posterior Triangle Group

The superior boundary of level V is the apex formed by the convergence of the sternocleidomastoid and the trapezius muscles, the inferior margin is the clavicle. The separation to the jugular groups is built by the posterior border of the sternocleidomastoid muscle or surgically by the plane built by the sensory branches of the cervical plexus. The posterior/lateral boundary is the anterior border of the trapezius muscle. Level VA and VB are separated by a horizontal plane through the inferior border of the cricoid cartilage. As prior described, the spinal accessory nerve and the transverse cervical vessels are at risk in level V. These lymph nodes are most commonly a metastatic target from nasopharynx and oropharynx cancers in sublevel VA and from the

Table 4 Boundaries of the neck levels [7]

Levels	Boundaries
I	Anterior: Contralateral anterior belly of the digastric muscle Superior: Mandible Posterior: Posterior belly of the digastric muscle Inferior: Hyoid bone IA: Submental lymph nodes between anterior bellies of digastric muscles IB: Submandibular lymph nodes posterior to the anterior belly of the digastric muscle
II	Anterior: Posterior belly of the digastric muscle Superior: Skull base Posterior: Posterior border of the sternocleidomastoid muscle Inferior: Horizontal plane through the hyoid bone IIA: Anterior to the spinal accessory nerve IIB: Posterior to the spinal accessory nerve
III	Anterior: Lateral limit of the sternohyoid muscle Superior: Horizontal plane through the hyoid bone Posterior: Posterior border of the sternocleidomastoid muscle Inferior: Horizontal plane through the inferior border of the cricoid cartilage
IV	Anterior: Lateral limit of the sternohyoid muscle Superior: Horizontal plane through the inferior border of the cricoid cartilage Posterior: Posterior border of the sternocleidomastoid muscle Inferior: Clavicle
V	Anterior: Posterior border of the sternocleidomastoid muscle Superior: Mastoid process Posterior: Anterior border of the trapezius muscle Inferior: Clavicle VA: Superior to a horizontal plane through the inferior border of the cricoid cartilage VB: Inferior to a horizontal plane through the inferior border of the cricoid cartilage
VI	Lateral: Bilateral carotid sheaths Superior: Hyoid bone Inferior: Suprasternal notch

thyroid gland cancers in sublevel VB. Skin cancers from behind the ear and parotid gland malignancies can spread to lymph nodes in level V.

Level VI, Anterior (Central) Compartment Group

The superior limit of Level VI is the hyoid bone and inferiorly it reaches the suprasternal notch. The lateral boundaries are the common carotid arteries. Pre- and paratracheal lymph nodes, the precricoid (Delphian) lymph node and the perithyroidal lymph nodes as well as the nodes along the recurrent laryngeal nerves are included in this level. The recurrent laryngeal nerves originate from the vagus nerve in the thorax and loop around the subclavian artery on the right side and the aortic arch on the left side. In the neck, the left recurrent nerve follows the tracheoesophageal groove longitudinally due to its low thoracic trajectory, while the right recurrent nerve approaches the midline with an approximate caudo-cranial angle of 30°. Cancers from the thyroid gland, glottic and subglottic larynx, apex of the piriform sinus and the cervical esophagus metastasize into lymph nodes in level VI.

Tables 4 and 5 summarize the different levels with their boundaries, contents and structures at risk.

Lymphatic Drainage Patterns According the Level System

The lymphatic drainage into the neck depends on the localization of the primary tumor and has been well demonstrated [8]. Table 6 summarizes the

Table 5 Neck level system with corresponding anatomical groups and structures at risk during neck dissection

Levels	Anatomical groups	Content/Structures at risk
IA and IB	Submental and submandibular group	• Facial artery and vein • Marginal mandibular branch of the facial nerve • Lingual nerve • Hypoglossal nerve
IIA and IIB	Upper jugular group	• Internal jugular vein • Internal and external carotid arteries • Spinal accessory nerve • Hypoglossal nerve • Vagus nerve
III	Middle jugular group	• Internal jugular vein • Common carotid artery • Superior thyroid artery • Vagus nerve • Phrenic nerve • Cervical plexus • Superior laryngeal nerve
IV	Lower jugular group	• Internal jugular vein • Subclavian vein • Common carotid artery • Transverse cervical vessels • Lymphatic thoracic duct • Vagus nerve • Phrenic nerve • Brachial plexus
VA and VB	Posterior triangle group	• Transverse cervical vessels • Subclavian vein • Spinal accessory nerve • Cervical plexus • Brachial plexus
VI	Anterior (central) compartment group	• Internal jugular vein • Common carotid artery • Recurrent laryngeal nerve • Oesophagus

Table 6 Level system lymph node drainage patterns from different sites of the head and neck region [7, 8]

Site	Levels
Oral cavity	I, II, III
Nasopharynx	II, III, IV, V
Oropharynx	II, III, IV
Hypopharynx	II, III, IV
Larynx	II, III, IV, VI
Parotid gland	II, III, VA
Thyroid/cervical trachea/cervical oesophagus	VI, VII, IV, III, II
Skin	I, II, III, IV, V

VII upper mediastinal lymph node level

lymphatic drainage patterns of the head and neck region using the level system described above in the chapter "Level system of cervical lymph nodes". By knowing these lymphatic drainage patterns, it allows to undergo more tailored neck dissections, decreasing their complications whilst obtaining optimal oncologic outcome.

Conclusion

The knowledge of the neck anatomy and lymphatic drainage patterns are essential in the planning and performing of a tailored and safe neck dissection. The surgical preparation should

follow known structures (vessels, muscles) and layers (fasciae) easy to dissect. Knowing the vital structures and their relation to landmarks are crucial for neck surgery. Upon exposure of a structure, the risk to injure the latter is decreased.

Self Study

1. **Contents within the carotid sheath are:**
   (a) Carotid artery
   (b) Hypoglossal nerve
   (c) Internal jugular vein
   (d) Vagus nerve
2. **A papillary carcinoma of the thyroid gland may metastasize primarily into the following levels of the neck:**
   (a) I, II
   (b) II, III, VA
   (c) II, VA
   (d) II, III, IV, VI, VII

Answers: Q1: (a), (c), (d); Q2: (d)

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Surgical Approaches and Operative Techniques for Cervical Lymph Node Pathology

Lluís Nisa, Adrian Schubert, Hergen Friedrich, and Roland Giger

Key Points

- Neck lymph node metastases are a major negative prognostic factor in head and neck squamous cell carcinoma
- Neck dissection is the mainstay of surgical therapy for nodal metastases from head and neck malignancies
- Good knowledge of the neck anatomy is essential to avoid iatrogenic injury in the course of neck dissection

Introduction

Historical Snippet and Nomenclature

The cervical lymph nodes constitute the defense frontline of infectious and neoplastic diseases of the upper aerodigestive tract. Consequently, they are the first metastatic target during regional spread of head and neck malignancies, particularly head and neck squamous cell carcinoma (HNSCCs) and thyroid cancer. Indeed, unlike other cancer types, HNSCCs are characterized by a relatively long loco-regional progression. Development of neck lymph node metastases is so far the most important prognostic factor, as presence of lymph node metastases reduces survival by approximately 50%. Management of lymph nodes is consequently a key element in the treatment of patients with HNSCC [1]. Surgical removal of lymph node levels potentially or actually affected by metastases leads to improved disease control. Surgical management of the neck lymph nodes for HNSCC encompass the systematic removal of such nodal groups along with surrounding fatty and connective tissue, and when required non-lymphatic structures.

While the importance of approaching the lymph nodes in the management of HNSCC was already recognized by several authors in the 19th century, the original standardized description of neck dissection (ND) is credited to George Crile in the early 20th century. In the original description, neck lymph nodes were removed ideally *en bloc* along with the internal jugular vein, the sternocleidomastoid muscle and the spinal accessory nerve. The major negative functional impact of systematic spinal accessory nerve resection was

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recognized, while the benefit of indiscriminate radical surgery became increasingly questioned [2]. As a result, since the 1960 s several authors proposed technical variants. Such developments along with the works assessing nodal levels at risk depending on the primary tumor site resulted in the description of standardized "nodal charts" which should be the object of surgical management. The nodal regions I to VI addressed in Chapter "Surgical Anatomy of the Neck" are the most widespread accepted [3–5]. Risk levels are established as follows:

- Levels I–III for oral cancers
- Levels II–IV for oropharynx, hypopharynx, supraglottis and glottis
- Levels II–V for the nasopharynx
- Level VI for the subglottis, thyroid, cervical trachea and cervical oesophagus.

The historical developments of surgical techniques and the recognition of levels at risk have resulted in the following standard nomenclatures of ND:

- Radical ND: classical operation, removing levels I to V along with the internal jugular vein, the sternocleidomastoid muscle and the spinal accessory nerve. Nowadays performed only if strictly dictated by the extent of nodal disease.
- Modified radical ND: technical variant of the classical radical ND sparing at least one of the three structures mentioned above. Medina proposed three types of modified radical ND to more precisely identify the preserved/removed structures [6]:
  - Type I: preservation of the spinal accessory nerve
  - Type II: preservation of the spinal accessory nerve and the internal jugular vein
  - Type III: preservation of the spinal accessory nerve, the internal jugular vein and the sternocleidomastoid muscle; this variant is also known as functional ND
- Extended radical ND (Fig. 1): entails a classical radical ND with removal of additional relevant non-lymphatic structures or lymphatic groups not usually removed during a radical

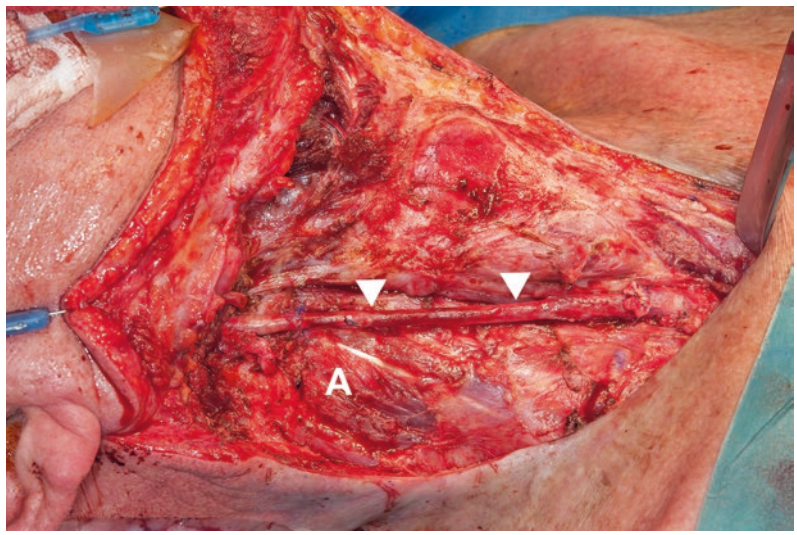

Fig. 1 Extended radical neck dissection (sacrificed sternocleidomastoid muscle, internal jugular vein and spinal accessory nerve) with additionally resected common carotid artery replaced by a greater saphenous vein graft (**Δ**) *(right side)*. **A** scalene muscles

ND. The most common structures that define an extended radical ND include:
  - The common, internal or external carotid artery
  - The vagus nerve
  - The hypoglossal nerve
  - The cervical and/or spinal plexus
  - The cervical skin
  - Parapharyngeal, buccinator or retropharyngeal lymph nodes
  - Parotid gland
  - Paratracheal lymph nodes
  - Upper mediastinal lymph nodes
- Selective ND: entails the removal of only some of the lymphatic levels of the neck. This technical variant is reserved for patients without manifest nodal disease (cN0) and takes into account the risk that a certain location of primary tumors gives to rise of metastases in certain levels (as mentioned above). Certain additional nomenclatures are used to describe the subtypes of selective ND based on anatomic regions addressed in Chapter "Surgical Anatomy of the Neck":
  - Supraomohyoid ND (levels I-III)
  - Lateral ND (levels II-IV)
  - Posterolateral ND (levels II-V)
  - Central compartment ND (level VI and sometimes VII).

Diagnostic Considerations—Staging of the Neck

In patients with cN0 nodal staging, management of the neck depends on the primary tumor site and stage. In such scenario, the neck may be treated prophylactically (either by surgery or irradiation) or regularly followed clinically and radiologically. Nevertheless, physical examination, imaging and staging of the primary tumor are not strongly predictive of neck lymph node involvement. Therefore, the management of the clinically negative neck (i.e. cN0 stage) in HNSCC is a topic of ongoing controversy. On one hand, final pathology of up to 20–30% of patients with cN0 nodal stage reveals occult lymph node metastases, but indiscriminate surgical management of all cN0 patients would lead to overtreat the remaining 70–80% of patients [7, 8]. In case of suspected lymph node disease, techniques to prove the diagnosis of metastases include fine needle aspiration cytology (FNAC), core needle biopsy (CNB) and diagnostic lymph node excision. It is important pointing out that if diagnostic excision is performed, the lymph node has to be removed completely and avoid capsular incision during the dissection to minimize the risk of neoplastic seeding. Moreover, diagnostic excisions should be performed only in case of doubtful diagnosis after attempted FNAC/CNB. Another alternative to assess regional lymph node status includes sentinel node biopsy (SNB), a strategy proposed to help in the decision-making process. SNB consists of harvesting the first lymph node relay, identified after peritumoral injection with a radioactive tracer or a blue dye, mainly in early cN0 oral cavity cancer patients. If histopathology reveals presence of metastatic involvement, a full ND must then be performed; otherwise the patient can be clinically followed [7, 9, 10].

A detailed discussion of the therapeutic approach to the neck in patients with HNSCC is beyond the scope of this chapter, but in broad terms, the following strategies are most commonly used:

- Surgical management of the neck along with the primary tumor, followed by radiation therapy with concomitant systemic therapy depending on the definitive pathological tumor staging
- Surgical management of the neck followed by irradiation of the primary tumor and the neck (i.e. up-front ND)
- Radiation with concomitant systemic therapy followed by surgery in case of incomplete response (i.e. salvage ND)

Surgical Management

Preoperative Considerations

Neck dissection is performed in total anesthesia, with the patient in supine decubitus, the neck in slight extension with the help of a shoulder roll, the head placed on a ring and turned contralaterally to the operated side in case of unilateral ND. Moreover, care has to be taken to minimize exposition of the neck to non-sterile areas such as the oral cavity or the pharynx in the course of simultaneous resection of primary tumors.

The likely extent of surgery has to be carefully evaluated by means of imaging, especially if bilateral ND is performed. This is essential since bilateral ligation of the internal jugular vein should be avoided to minimize the risk of massive soft tissue edema and potentially intracranial hypertension. If bilateral ND is performed, a protective, temporary tracheostomy should be considered.

Finally, it is important to discuss with the anesthesist regarding muscle relaxation if electrical neurostimulation for nerve monitoring is used intraoperatively.

Operative Technique

The surgical steps of modified radical ND are going to be described in the next paragraphs; systematically from levels I to V. Central ND (level VI) described afterwards, separately. It should be noted that such systematic description does not necessarily correspond to the actual execution of ND, since factors like disease extent, intraoperative findings and surgeon's preferences result in variations of the specific steps. Figures 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 and 17 show step-by-step the preferred sequence of a modified radical ND (level I–V) performed by the senior author (RG). Figure 18 shows the dissection of the central neck level VI. Each level may be dissected and sent to the histopathology laboratory separately to obtain a precise level-specific mapping of nodal disease, which allows better-tailored radiotherapy if indicated postoperatively.

Incision and preparation of the platysma flap **(Figs. 2–4)**

The anatomical landmarks ought to be marked prior to the incision, especially the mandibular angle and the lower rim of the mandible. Incision should run at least 3 cm caudal to the latter to avoid injury of the marginal mandibular branch

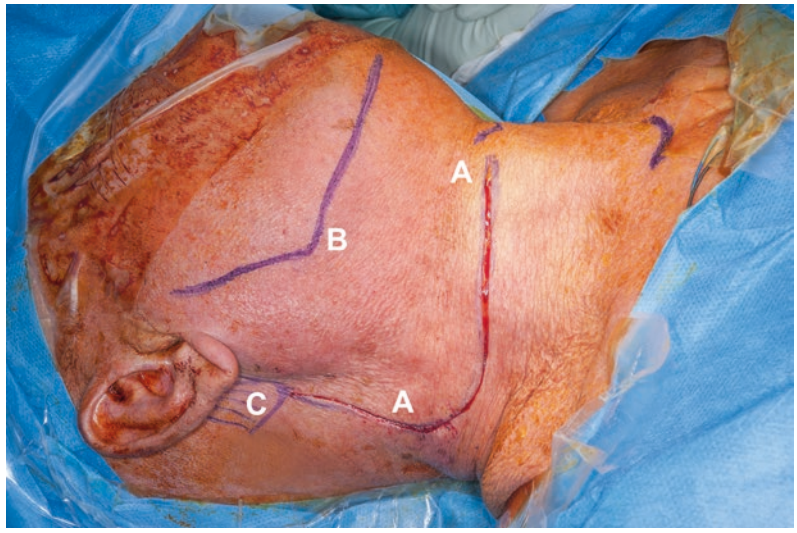

Fig. 2 J shaped skin incision for lateral neck dissection (**A**) *(right side)*. **B** inferior border of the mandible, **C** mastoid tip

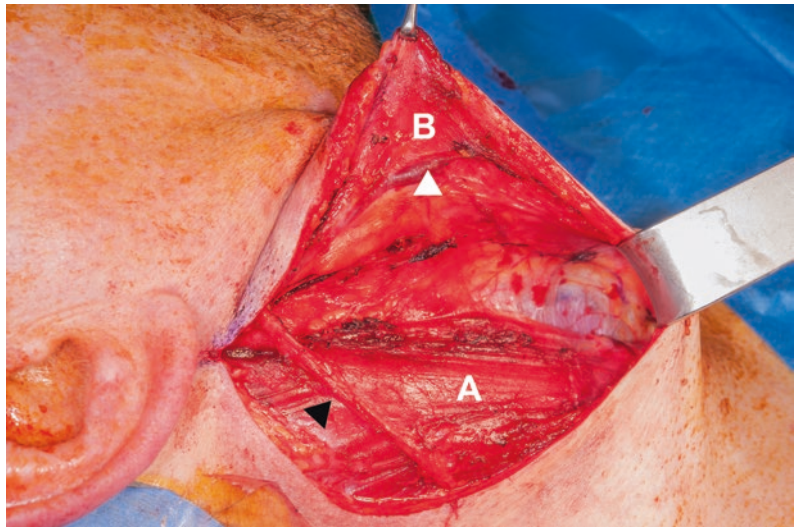

Fig. 3 Dissection and development of subplatysmal flap anteriorly and posteriorly *(right side)*. **A** sternocleidomastoid muscle, **B** platysma, Δ ligated and divided external jugular vein, ▲ greater auricular nerve

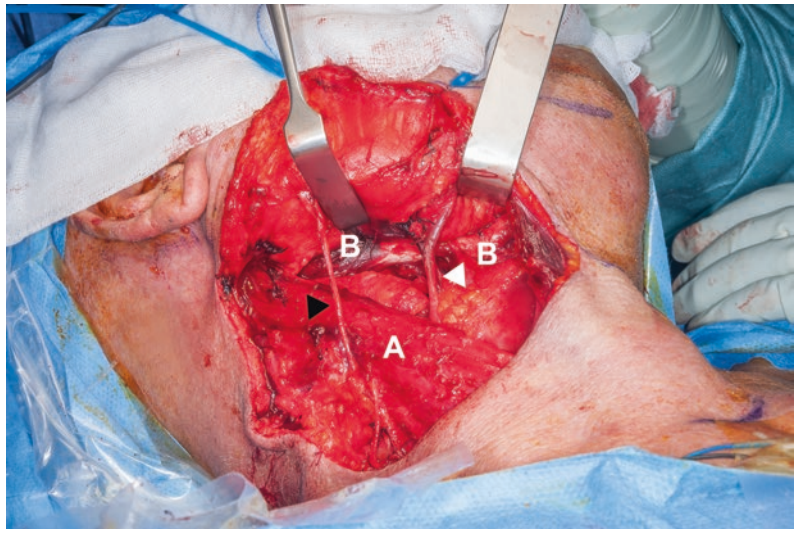

Fig. 4 Dissection of the fascia covering the anterior and posterior belly (**B**) of the digastric muscle *(right side)*. The Langenbeck and Farabeuf retractor lift up the submandibular gland. **A** sternocleidomastoid muscle, **Δ** facial vein, ▲ greater auricular nerve

of the facial nerve. For a unilateral ND, the incision ought to run from the ipsilateral mastoid to the midline of the neck; for a bilateral ND, from one mastoid to the contralateral one. Infiltration of the skin with a local anesthesia and/or diluted adrenalin can be performed prior to incision.

Many types of incision have been historically used/suggested, including the apron/half apron, single or double Y, H, or the MacFee's parallel incisions among others. Currently, the half apron incision is preferred (for unilateral ND),

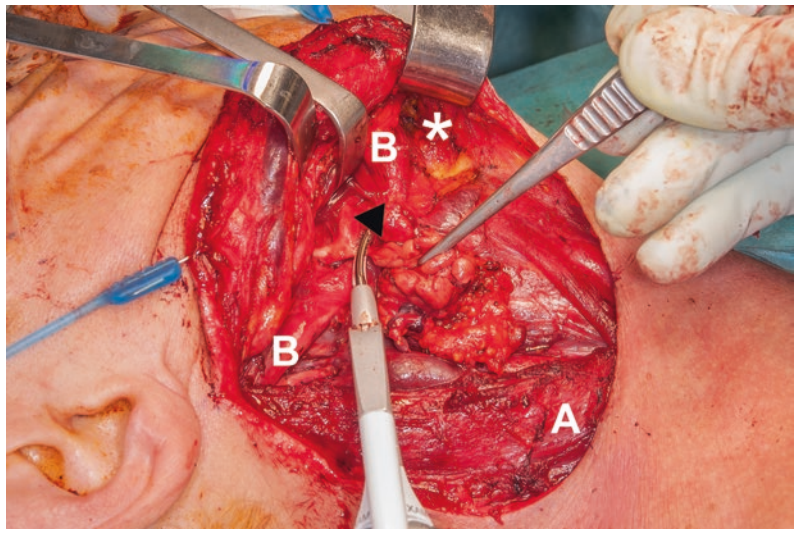

Fig. 5 Dissection of the submental (*, level IA: between the two anterior bellies of the digastric muscles from both sides) and submandibular triangle (level IB: between the anterior and posterior belly of the ipsilateral digastric muscle) *(right side)*. Separation of the submandibular gland retracted inferiorly by the forceps from the exposed lingual nerve (▲). The submandibular branch of the facial nerve is gently retracted by the upper Farabeuf retractor. **A** sternocleidomastoid muscle, **B** anterior and posterior belly of the digastric muscle

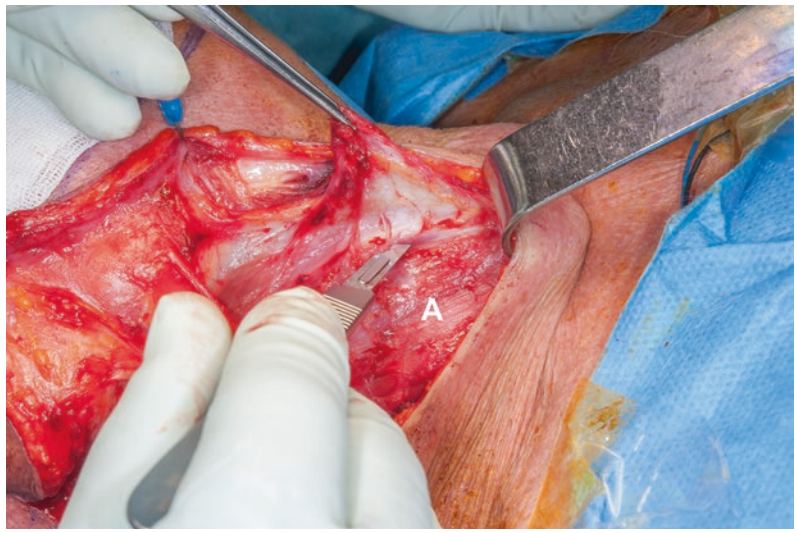

Fig. 6 Dissection of the fascia covering the sternocleidomastoid muscle (**A**) *(right side)*

while discharge incisions and multiple, disconnected incisions are to be avoided to decrease the risk of skin necrosis. A further consideration to decide the kind of incision is whether the primary tumor is approached at the same time as ND. For instance, if laryngectomy and/or pharyngectomy are performed along with ND, a U-shaped (apron) incision joining both mastoids

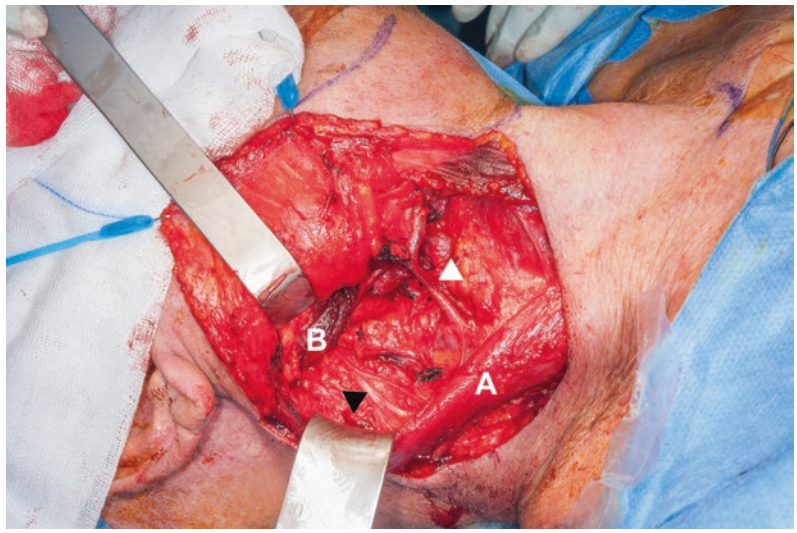

Fig. 7 Dissection of the spinal accessory nerve (▲) *(right side)*. **A** sternocleidomastoid muscle, **B** posterior belly of the digastric muscle, **Δ** facial vein

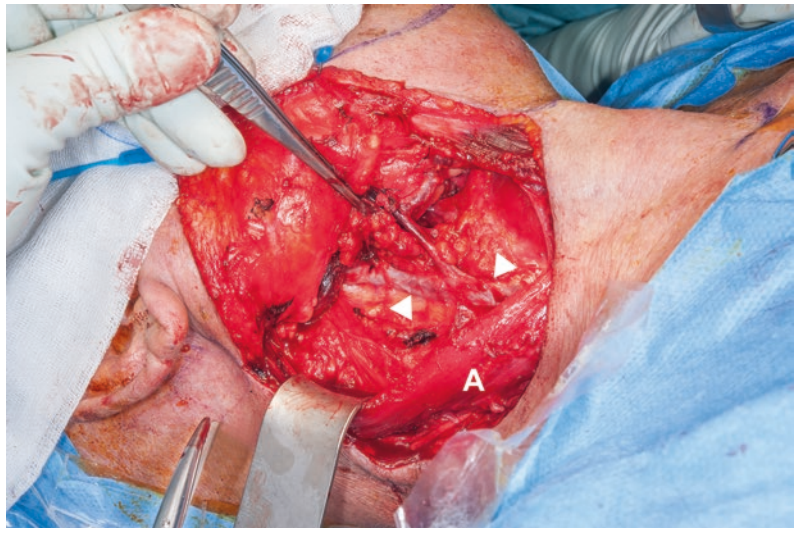

Fig. 8 Division of fibrofatty tissue of level IIA (retracted anteriorly by the forceps) overlying the internal jugular vein (**Δ**) *(right side)*. Dissected tissue is brought anteriorly and posteriorly. **A** sternocleidomastoid muscle

and caudally reaching the site of the future tracheostoma is preferred.

The next step consists in preparing the skin-platysma flap caudally and cranially. The external jugular vein is often ligated, while the greater auricular nerve ought to be preserved when possible. In the course of cranial preparation of the skin-platysma flap, care should be taken not to injure the marginal mandibular branch of the facial nerve. For this purpose, it

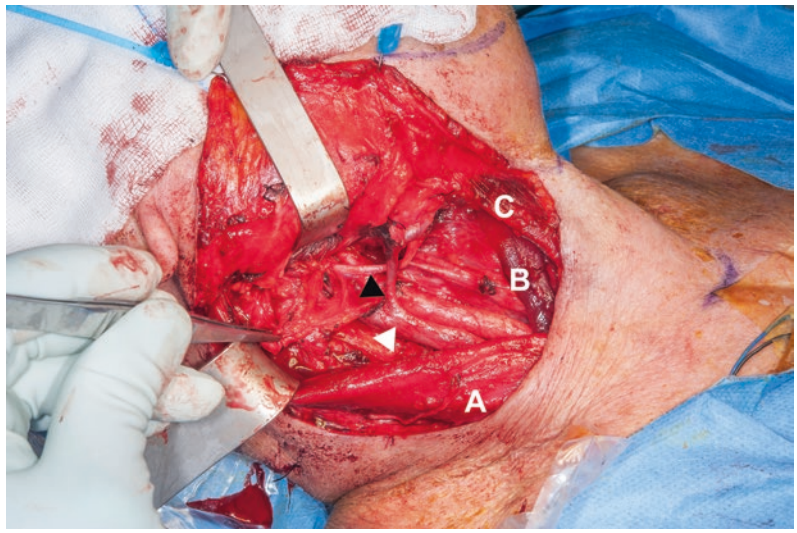

Fig. 9 Fibrofatty tissue dissection of the levels II and III from anterio-superior to posterio-inferior by exposing and freeing the underneath muscles and neurovascular bundle (Δ internal jugular vein, common carotid artery, vagus nerve) *(right side)*. **A** sternocleidomastoid muscle, **B** omohyoid muscle, **C** sternohyoid muscle, ▲ hypoglossal nerve

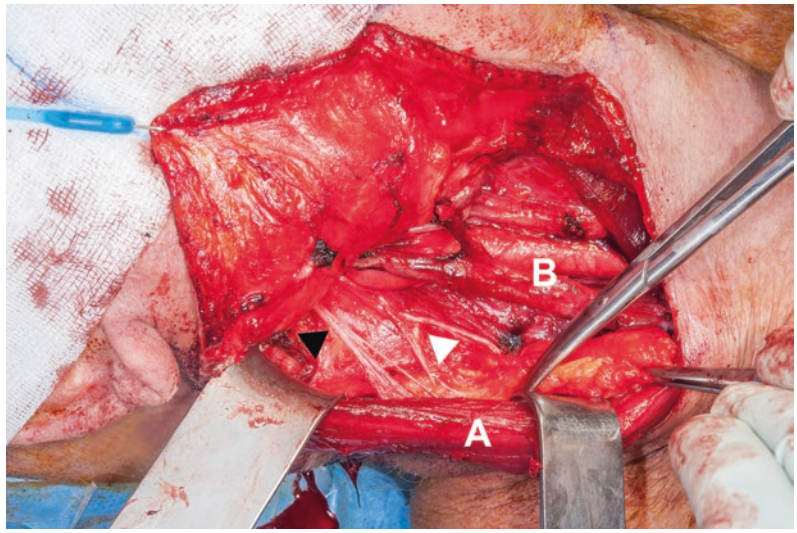

Fig. 10 Fibrofatty tissue dissection of the level III and tissue stripping off the cervical plexus branches (Δ) *(right side)*. **A** sternocleidomastoid muscle, **B** neurovascular bundle containing internal jugular vein, common carotid artery and vagus nerve, ▲ spinal accessory nerve

is important to elevate the cranial aspect of the platysma superficial to the submandibular gland. The marginal mandibular branch lies right below the superficial fascia and can be visually identified. Incision of the superficial fascia should be performed at the inferior aspect of the

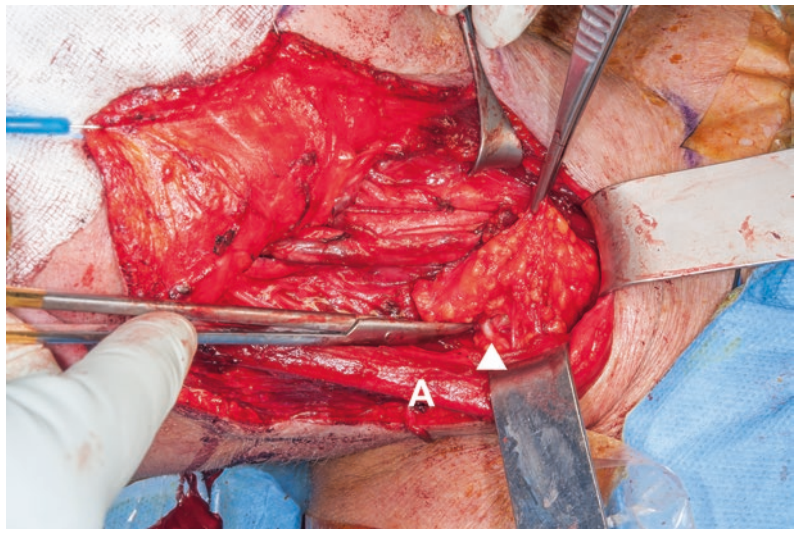

Fig. 11 Dissection of the level IV containing fibrofatty tissue, thoracic or right lymphatic duct and transverse cervical vessels (**Δ**) *(right side)*. Preservation of the vagus nerve, phrenic nerve and brachial plexus. **A** sternocleidomastoid muscle

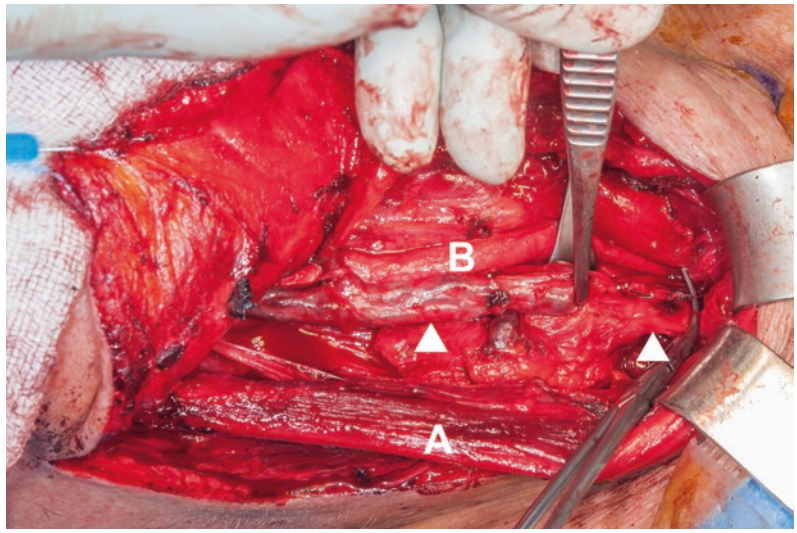

Fig. 12 Modified radical neck dissection indicated by inferiorly adherent lymph node metastases to the internal jugular vein (**Δ**) *(right side)*. Ligation and division of the internal jugular vein inferiorly and superiorly (**Δ**). Separation of the specimen from the common carotid artery (**B**) and vagus nerve. **A** sternocleidomastoid muscle

submandibular gland, or if the nerve is identified, parallel to it in order to elevate the latter with the platysma flap, hence avoiding its injury during dissection of the submandibular gland. The marginal mandibular branch is superficial to the facial vessels, so in case of doubt, a

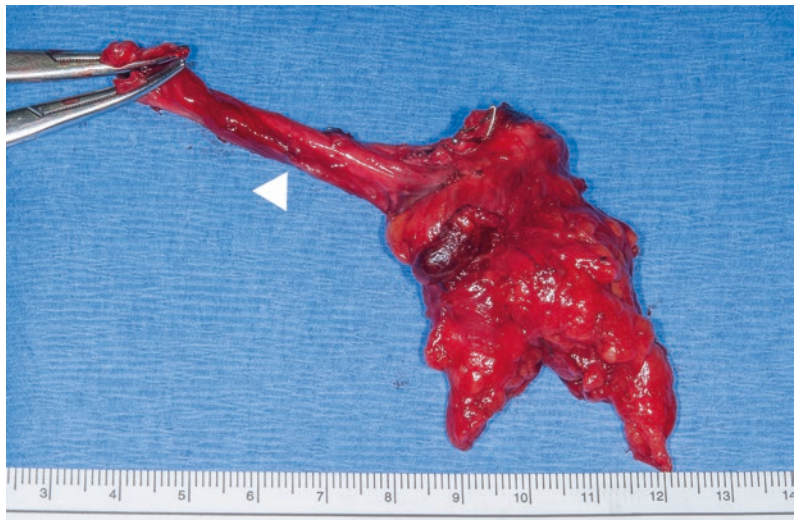

Fig. 13 Dissected specimen level IV with adjacent internal jugular vein (Δ)

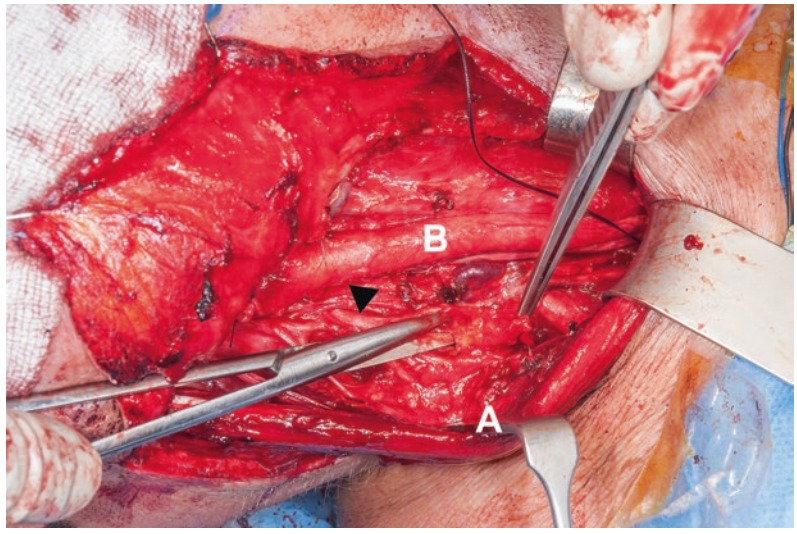

Fig. 14 Fibrofatty tissue dissection of the levels VA and VB behind the cervical plexus branches (▲) *(right side)*. The internal jugular vein has been ligated inferiorly and superiorly, and resected. **A** sternocleidomastoid muscle, **B** common carotid artery with vagus nerve posteriorly

further strategy consists of searching the facial vein posterior to the submandibular gland and proceeding dissection deep to the vein, either by keeping or ligating this vessel.

The extent of caudal preparation of the skin-platysma flap is determined by the type of ND performed. Typically, for a modified radical ND the flap is elevated down to the clavicle.

Dissection of levels IA and IB **(Fig. 5)**

The digastric muscle and most particularly its anterior belly is an extremely useful landmark for dissection of level I (the posterior belly will be useful to identify the spinal accessory nerve at a later stage). Indeed, the hypoglossal nerve lies deep to the muscle and its exposition allows caudal preparation of the submandibular

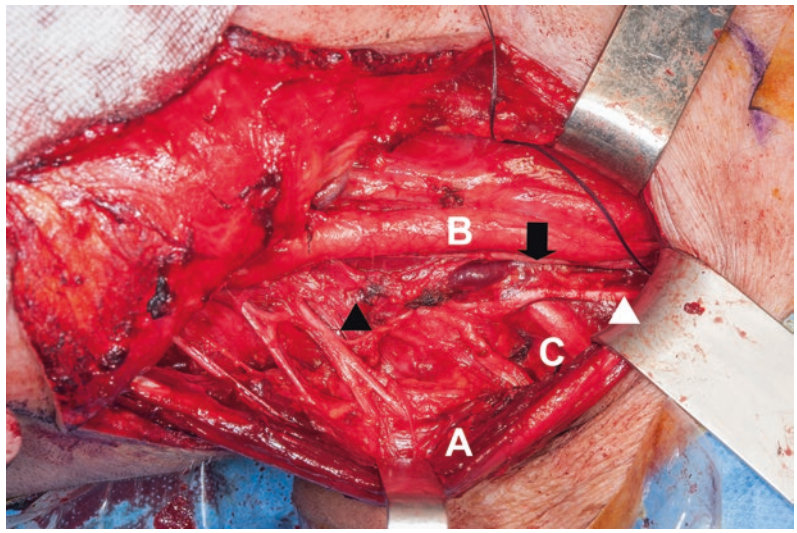

Fig. 15 Modified radical neck dissection of the levels IIA, IIB, III, IV, VA and VB *(right side)*. The internal jugular vein has been removed. Dissection of the level I needs still to be performed to complete the surgery. **A** sternocleidomastoid muscle, **B** common carotid artery with vagus nerve posteriorly (↓), **C** brachial plexus, ▲ cervical plexus, Δ phrenic nerve

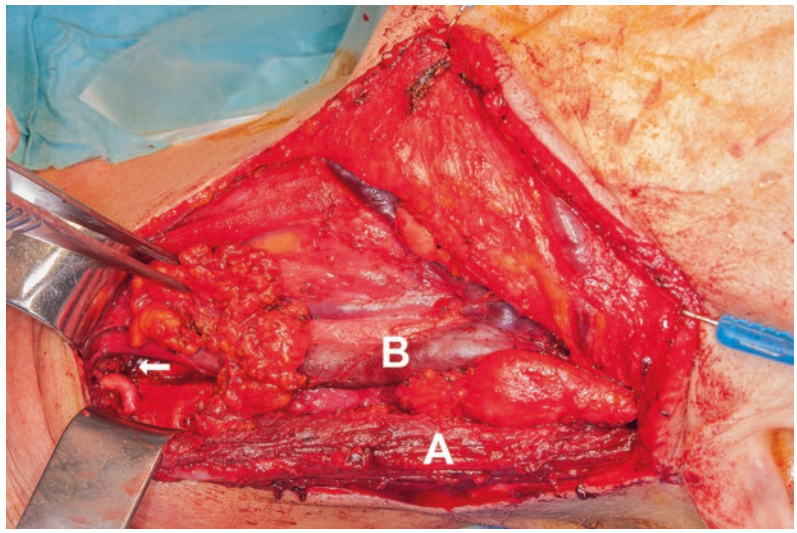

Fig. 16 Fibrofatty tissue dissection of the level IV on the *left side* with exposed part of the thoracic duct (⇐). Between the sternocleidomastoid muscle (**A**) and the internal jugular vein (**B**) superiorly, a lymph node metastasis in level IIA has been exposed

gland. The capsule of the submandibular gland (a part of the superficial fascia, see Chapter "Surgical Anatomy of the Neck") is followed cranially in a subcapsular manner, to avoid lesion of the marginal mandibular branch of the facial nerve. Separation of the gland from the facial vein (posteriorly) and the facial artery (cranial and posteriorly) usually allows mobilization of the gland. For its anterior mobilization, the mylohyoid muscle is separated from

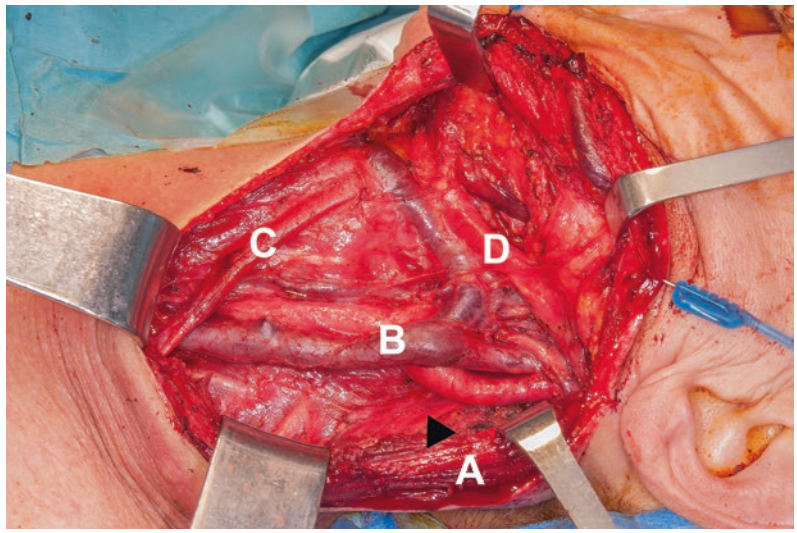

Fig. 17 Completed modified radical neck dissection (level IA–VB) with preservation of the sternocleidomastoid muscle (**A**), the internal jugular vein (**B**) and the spinal accessory nerve (retracted by the posterior Farabeuf retractor beneath the ear) *(left side)*. **C** omohyoid muscle, **D** posterior belly of the digastric muscle, ▲ cervical plexus

the gland and retracted ventrally. Due to the rich vascularization of this particular region, prophylactic cautery should be considered for anterior preparation of the gland. Upon full anterior and posterior mobilization of the gland, further dissection in the depth is performed on the cranial aspect of the gland by pulling the latter downwards. Care has to be taken not to injure the lingual nerve, typically recognized by its elbow-like shape. The submandibular duct should be ligated to avoid retrograde contamination from the oral cavity. Now level IB dissection is completed by removing the gland and dissecting the fatty tissue up to the insertion of the anterior belly of the digastric muscle. For dissection of level IA, the anterior belly of the digastric muscle is followed ventrally and the contralateral muscle is identified and equally prepared. Subsequently, the fatty tissue contained between the anterior digastric bellies and the hyoid bone is separated from the mylohyoid muscle in the depth and removed *en bloc*.

Dissection of lateral (IIA/IIB–IV) and posterior levels (VA/VB) **(Figs. 6–17)**

Dissection of the lateral neck levels entails identification and preparation of the anterior border of the sternocleidomastoid muscle. This specific step is usually performed, at least partially, early during the ND while preparing the platysma flap. The key landmark is the posterior belly of the digastric muscle, since both the spinal accessory and the hypoglossal nerve lie deep to the muscle, so that dissection is safe as long as performed superficial to this landmark. The hypoglossal nerve is prepared and retracted along with the digastric muscle. The latter is followed posteriorly to the level of the internal jugular vein. The spinal accessory nerve is most often found between the posterior belly and the internal jugular vein, but it can sometimes be found posterior to the internal jugular vein. The spinal accessory nerve enters the sternocleidomastoid muscle in the depth and exits it posteriorly, penetrating the trapezius muscle some 5 cm cranial to the clavicle. For this reason, preparation of the posterior border of the sternocleidomastoid muscle can equally result in injury of the spinal accessory nerve. Level IIA lays anteriorly and level IIB posteriorly to the spinal accessory nerve. For removal of level IIB, deep dissection down to the prevertebral fascia is performed at the upper aspect of the ND and subsequently preparation proceeds caudally. At the uppermost aspect of the neck, the occipital artery (a branch of the external carotid artery running opposite the facial artery) crosses the internal jugular vein and is

often injured unless prophylactically cauterized. Further dissection downwards requires identification of the internal jugular vein and its separation from the surrounding fascia (the carotid sheath, see Chapter "Surgical Anatomy of the Neck"). Subsequently analogous identification of the common, internal and external carotid arteries, as well as the vagus nerve is performed (neurovascular bundle). The inferior root of the ansa cervicalis is usually found medial to the internal jugular vein, either superficial or deep, and should be preserved when possible. During the caudal preparation of the sternocleidomastoid muscle and the neurovascular bundle, the omohyoid muscle is identified and should equally be prepared and retracted to liberate the vessels and vagus nerve down to the clavicle level. The boundary between level III and IV is a horizontal plane through the inferior border of the cricoid cartilage. Gentle retraction of the vessels and nerve is applied to dissect the fatty tissue surrounding these structures. Anteriorly the tissue needs to be separated from the strap muscles to complete dissection. Posteriorly to the vessels the branches of the cervical plexus delimit the plane separating the posterior levels (VA and VB), and when possible, they should be preserved. Dissection of level IV, especially on the left side, should be carefully performed to avoid injury of the lymphatic thoracic duct. Also in the caudal aspect of the ND (during removal of levels IV and VB), injury of the phrenic nerve may occur. The latter runs parallel, lateral and posterior to the vascular axis, and ventral to the anterior scalene muscle. Upon identification of these structures, the fatty tissue superficial to the scalene muscles is removed to complete level V dissection.

In cases requiring removal of the internal jugular vein (with or without the sternocleidomastoid muscle), it should be prepared keeping some distance from the tumoral mass and ligated at both extremities.

Central neck dissection (level VI) **(Fig. 18)**
Given that central compartment ND is mostly indicated in case of differentiated thyroid carcinomas, it is often combined with a thyroid approach (hemithyroidectomy/total thyroidectomy). In the course of the above mentioned surgery, the recurrent laryngeal nerve (RLN) should be preserved, especially if preoperatively intact (evaluation by laryngoscopy). On

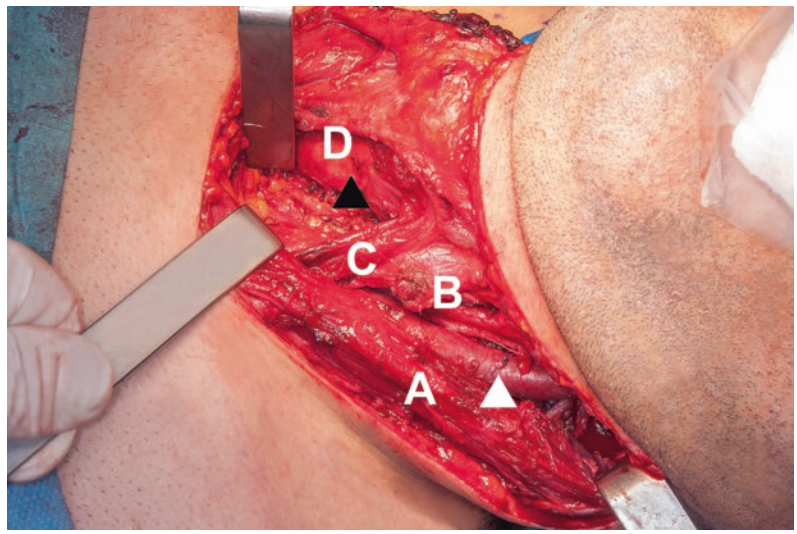

Fig. 18 Fibrofatty tissue dissection of the level VI on the *left side* through an anterior approach by gently retracting the trachea to the right side by the Langenbeck retractor and retracting the sternohyoid together with the sternothyroid muscle laterally by the Farabeuf retractor. The recurrent laryngeal nerve (▲) has been freed off the surrounding fibrofatty tissue. **A** sternocleidomastoid muscle, **B** omohyoid muscle, **C** sternohyoid and sternothyroid muscles, **Δ** internal jugular vein, **D** trachea

the right side, the RLN approaches the midline with an approximate angle of 30°, while on the left side it runs parallel to the tracheoesophageal groove. Ideally, parathyroid gland tissue should be preserved to decrease the long-term morbidity induced by hypoparathyroidism. For central compartment dissection, the fatty tissue between the neurovascular bundle (common carotid artery, vagus nerve, internal jugular vein) and the tracheoesophageal groove is dissected up to the hyoid bone and caudally to the upper mediastinum. The lower boundary for a central ND is often ill defined, since no clear anatomical landmark separates the fatty tissue of the lower neck from that of the upper mediastinum. Importantly, for subglottic carcinomas the level VI should equally be dissected.

Outlook: Developing Techniques

To avoid the cosmetic impact of open approaches to the neck, minimally invasive technical variants have been described, including endoscopic and robot-assisted ND.

Several authors have established the safety and feasibility of robotic selective ND in patients with cN0 disease via a modified facelift, retroauricular, submandibular or transaxillar approach, or combinations thereof. Most authors report a significantly longer time of surgery when compared to conventional ND, but similar nodal yield and improved cosmetic results, without significantly different complication rate [11–14]. Systematic comparison of oncological outcomes between these minimally invasive techniques and conventional ND is essential before establishing the role of this novel technique.

Perioperative Accidents

Injury to Vascular Structures

The neck tissues are richly vascularized and during ND ubiquitous bleeding from small vessels is common and can be easily managed by electrocautery or any other standard methods. While such bleedings are not problematic in hemodynamic terms, they can impair proper visualization of important structures and facilitate iatrogenic injury. An illustrative example is the venous plexus around the hypoglossal nerve (ranine veins), which require prophylactic cauterisation to avoid diffuse bleeding and difficult visualization of the nerve.

Injury of bigger vessels and in particular of the internal jugular vein or the carotid artery (or one of its major branches) can quickly lead to hemodynamic instability, if not quickly addressed. Small injuries of these vessels can be managed by suture or ligation. In case of a big size injury of the internal jugular vein, it can be ligated, usually without major problems. Ligating the common or internal carotid arteries carries a risk of neurovascular complications. In this respect, the importance of preoperative evaluation of tumors potentially infiltrating these vessels by means of a balloon occlusion test has to be stressed.

Injury to Nerve Structures

Given the complex anatomy of the neck and the presence of multiple nervous structures, including portions of 5 cranial nerves (CN V3, CN VII, CN X–XII) as well as the cervical and brachial plexus, nerve injury ranges among the commonest complications of ND.

The following nerve lesions can be seen as a complication of ND:

Marginal mandibular branch of the facial nerve: Its injury manifests with paralysis of the orbicularis oris muscle and especially of the ipsilateral mouth commissure. When isolated, it rarely results in severe functional impairment with drooling and oral incontinence especially by fluid intake. This nerve is most at risk when the platysma flap is raised cranially and again during preparation of level IB.

Lingual nerve (branch of CN V3): This nerve can be injured both during cervical and transoral mouth floor approaches. The lingual nerve is most at risk during ablation of level IB,

especially while preparing the postero-medial aspect of the submandibular gland. Its injury result in hypoesthesia, in some cases with associated dysesthesia of the anterior two thirds of the tongue. Moreover, the lingual nerve is connected to the facial nerve via the chorda tympani, supplying special sensory gustative afference to the same region.

Hypoglossal nerve: Sole responsible for efferent motor innervation of the tongue muscles, both extrinsic and intrinsic (excepting the palatoglossal muscle). Its injury leads to paralysis of the ipsilateral hemitongue. The joining tendon of the digastric muscle is an important landmark to avoid injury of this nerve.

Spinal accessory nerve: Its injury leads to paralysis of the trapezius muscle with progressive inability to raise the shoulder and to extend arm abduction beyond 90°. Moreover, partial or complete spinal accessory nerve lesion may lead to chronic pain of the shoulder. If not properly identified and actively managed by physiotherapy, spinal accessory nerve lesion may in time lead to severe functional impairment of the shoulder, a clinical scenario known as "frozen shoulder" with a profound impact on patients' quality of life [15, 16].

Phrenic nerve: Its injury leads to ipsilateral paralysis of the diaphragm.

Other Peri- and Postoperative Complications

Chyle Leak

Chyle leaks result from iatrogenic injury to the thoracic duct during ND or thyroid surgery. Most leaks occur on the left side due to the course of the thoracic duct and manifest post operatively with a milky fluid through the drainage or with swelling of the supraclavicular region. Chyle leak may result in severe electrolyte disturbances and loss of protein. If milky, but often transparent fluid is seen in the course of surgery of level IV, ligature of the thoracic duct should be immediately attempted. In case the chyle leak is identified after surgery, the management may primarily be conservative, consisting of a parenteral nutrition, low-fat diet as well as application of a compressive dressing for approximately 1 week. A persistent leak may require surgical exploration if conservative measures fail. Some authors advocate for early intervention in such scenarios [17]. In exceptional cases, more aggressive management strategies such as a flap or a thoracic approach with ligation of the thoracic duct may be needed. Percutaneous transabdominal embolization after the cisterna chyly can be considered as an alternative [18, 19]. Although a rare complication, chyle leaks carry substantial morbidity, imposing awareness on this condition and a high suspicion index among head and neck and thyroid surgeons.

Seroma

A seroma is a collection of serous fluid within a surgical cavity following surgery. Its prevalence following neck surgery ranges between 3 and 7%. Seromas are usually managed conservatively, eventually by ultrasonography-guided aspiration and compressive dressing, but in some cases surgical revision is needed [20].

Conclusion

Neck dissection is the mainstay surgical management procedure for regional lymph node involvement in cancers of the head and neck region. Removal of cervical nodal levels implies systematic approach and good knowledge of the neck anatomy, which are essential in order to improve prognostic and avoid iatrogenic injury, which in turn may have a profound effect on patients' oncological outcome and quality of life.

Self-study

1. **In the course of a modified radical neck dissection, the following structures are spared:**
   (a) The spinal accessory nerve
   (b) The internal jugular vein
   (c) The sternocleidomastoid muscle
   (d) At least (a), possibly with (b) and/or (c).
2. **One of the following structures is NOT at risk during dissection of levels I to III:**
   (a) The spinal accessory nerve
   (b) The lingual nerve
   (c) The submandibular duct
   (d) The recurrent laryngeal nerve.

Answers: Q1: (d); Q2: (d)

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Mediastinal Lymphatic System

Embryology and Surgical Anatomy of the Mediastinal Lymphatic System

Claudiu E. Nistor, Adrian Ciuche, and Ecaterina Bontaș

Key Points

- Describe embryological basis and typical anatomy of the thoracic duct.
- The existence in the embryonic period of both right and left thoracic ducts explains the presence of numerous variations in the origin, path, flow and ends of the thoracic duct.
- The thoracic duct drains the lymph from entire body excluding the right part of thorax, the right upper member, and right parts of the head and neck.

Introduction

When the human embryo is about 10 mm in length, the lymphatic system emerges with its development [1]. Usually, it provides the most important lymphatic vessels of our body known as the thoracic duct (left thoracic duct) and the right thoracic duct. As such, the thoracic duct assures about 80% of the lymph created in the body to the venous circulation [2]. Importantly, the injury of thoracic duct is most commonly found in esophageal resections for esophageal cancer.

Embryology of the Lymphatic System

The lymphatic system originates from the lateral mesoderm by developing the lymphatic buds which originate from the inner layer of the nearby veins (Fig. 1) [3]. This evolutionary process begins at the end of the fifth week of embryonic development, about two weeks later than the cardiovascular system. There are 6 primary lymphatic buds named two jugular lymph sac, two iliac lymph sacs, one retroperitoneal lymph sac, and one lymph sac that will develop the cisterna chyli [1]. During the embryological development by the caudal growth of the jugular buds and cranial cisterna chyli, and by joining them, a structure is emerging from which the future thoracic duct will also be born [4–7].

Accordingly, the existence in the embryonic period of both right and left lymphatic ducts explains the presence of numerous variations in the origin, path, flow and spill of the thoracic

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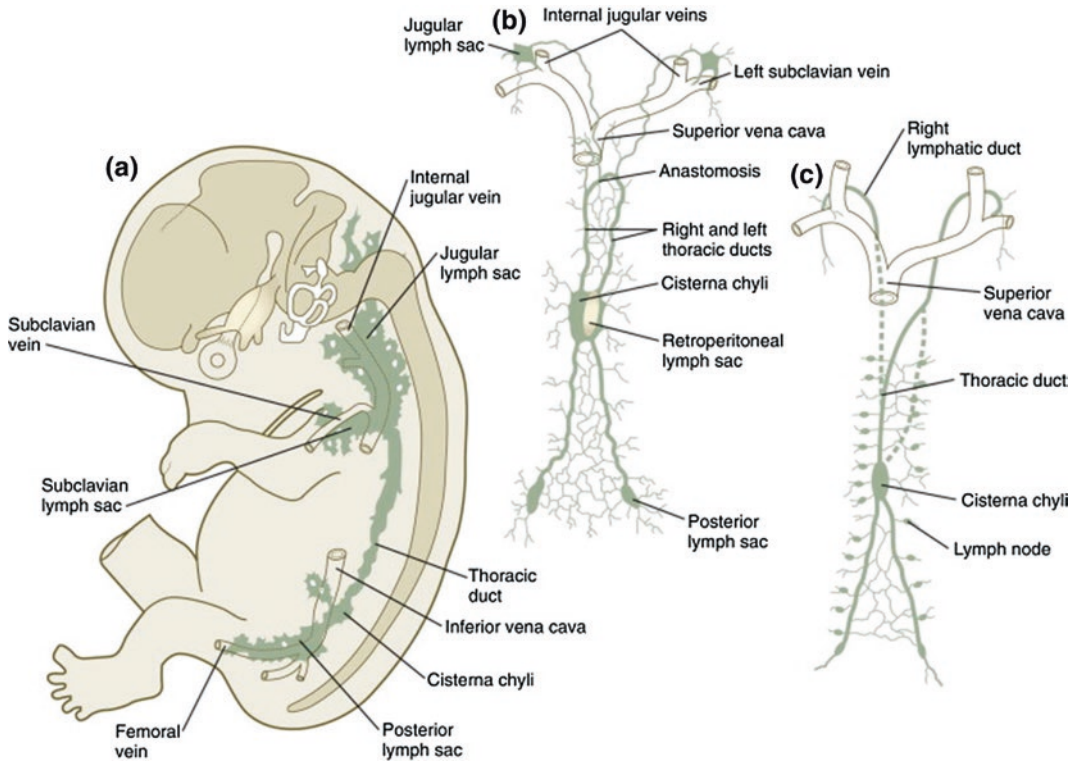

Fig. 1 Stages in the development of the major lymphatic channels. **a** and **b** show 9-week-old embryos. **c** shows the fetal period. Between **b** and **c**, the transformation between the reasonably symmetrical disposition of the main lymphatic channels and the asymmetrical condition that is characteristic of an adult can be seen. From [3] with permission

duct. It has to be underlined that left lymphatic duct is known as the thoracic duct.

During fetal maturation, the definitive thoracic duct is effectively forming from the caudal part of the right thoracic duct (2/3 lower), the cranial part of the left thoracic duct (1/3 upper) and from the anastomoses between both lymphatic ducts. The other segments (1/3 upper right thoracic duct and 2/3 lower left thoracic duct) are obliterated. That is how it is established the configuration of the adult thoracic duct itself.

The right lymphatic duct derives from the cranial part of the right embryonic thoracic duct when it is not obliterated. The spill of the right lymphatic duct and the right thoracic duct (when this anatomical variant exists) occurs at the level of confluence of the right internal jugular vein and right subclavian vein.

Histology of the Lymphatic System

The origin of the lymph comes from the interstitial fluid or space which in turn comes from the lymphatic capillaries (Fig. 2) [8]. The return of lymph into blood flow is via the venous and lymphatic systems. In general, the structure of the lymphatic system is represented by lymphatic capillaries, lymphatic vessels, lymph nodes and lymphoid trunks grouped into lymphatic collectors.

The fluids and macromolecules of the body pass from the interstitial space into the lymphatic circulation through the lymph capillaries, the latter representing the origin of the lymphatic system. Interstitial space contains the interstitial fluid with chemical composition similar to plasma filtration formed by filtration in the arteriolar segment of the capillary, and is absorbed continuously at the level of the venous

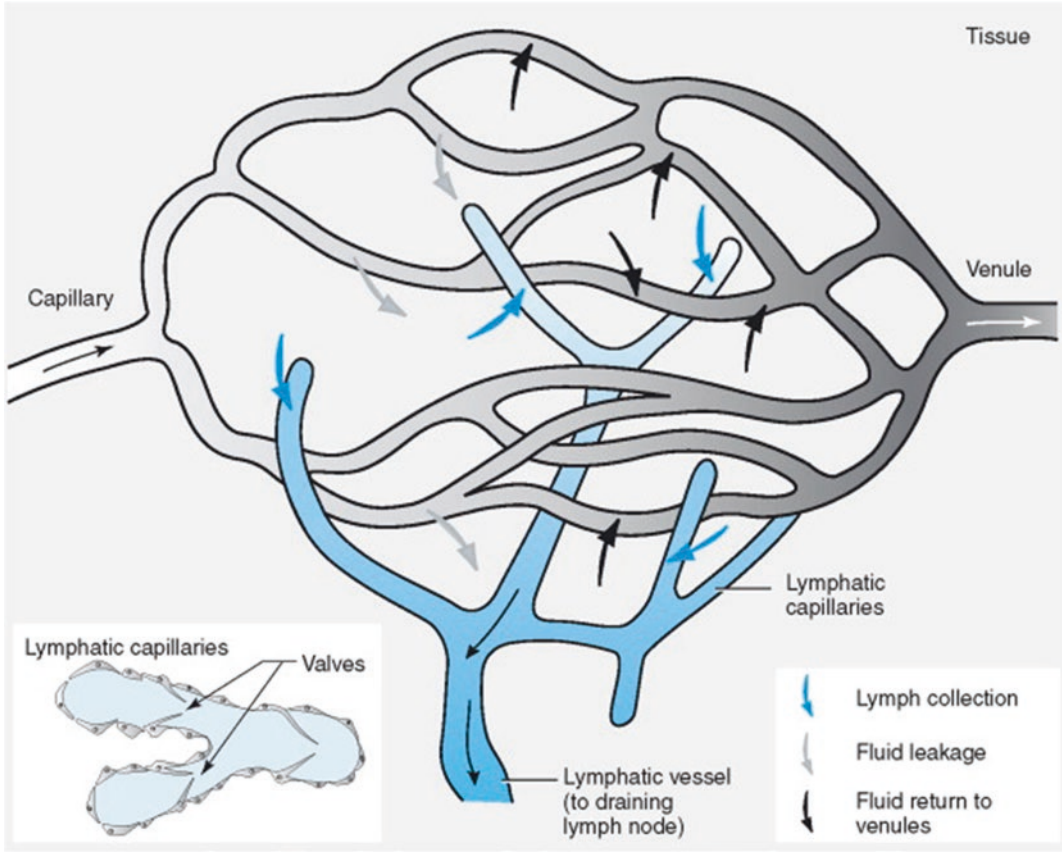

Fig. 2 The collection of lymph in peripheral tissues. Most of the fluid that leaks from the capillaries into the tissues is taken up by the venules, but the remainder seeps back into the lymphatic vessels, which are blind-ended, finger-like protrusions intertwined with the blood capillaries. The overlapping structure of the endothelial cells creates specialized pores that allow high molecular weight substances (proteins, fats, leukocytes, and even microbes) to pass into the lymphatic capillaries. Valves are present in all lymphatic channels to ensure the unidirectional flow of lymph into the collecting lymphatics (insert). The lymphatic vessels lead to local draining lymph nodes and ultimately flow into the thoracic duct, which empties the lymph back into the blood circulation. From [8] with permission

end. However, the absorption capacity is limited and only a small amount of 1/10 of this fluid is removed at this level via the lymphatic system [9, 10].

There are some features of lymphatic vessels that distinguish them from blood capillaries. The lymph capillary wall consists of a single layer of endothelial cells, thinner and more flattened than those present in blood capillaries; and the basal membrane is missing, which allows large molecules to easily cross the wall. Also, lymphatic capillaries have blind endings, being practically free of arterial or venous connections. The lymphatic capillaries have no pericytes (contractile cells with role in regulating the blood flow through blood capillaries). At the level of lymph capillaries, there are filaments attached to endothelial cells that basically anchor lymphatic capillaries to interstitial connective tissue, having a role in preventing lymphatic capillary collapse when interstitial fluid pressure increases (interstitial edema).

Lymphatic capillaries are found in almost all tissues of the body, except for the ocular, central nervous system and avascular tissues (epidermis, cartilage, muscle endomysium, etc.).

The main lymphatic trunks, such as the thoracic duct (left thoracic duct) and the right

lymphatic duct have a histological structure similar to veins of the same size (Fig. 3) [8]. The thoracic duct (also known as Van Hoorne's canal) is the largest lymphatic vessel in the body, having about 0.5 cm in diameter and 40 cm in length. Its wall has three tunics: intima, media and externa. Intima tunic ('inner coat') contains vascular endothelium, a well-developed basal membrane and elastic connective fibers. Media tunica is well developed and contains smooth muscle fibers and elastic connective tissue, having a role in maintaining the lymph flow through its rhythmic contractions. External tunic or tunica adventitia contains smooth muscle fibers and vasa vasorum.

In the normal adult, the thoracic duct can carry approximately 4 liters of lymph fluid daily, made up of ***lymph*** (rich in proteins, electrolytes and water; derived by capillary filtration process of capillaries from the neighbour of lymphatic capillaries), which add ***lymphocytes*** and ***immunoglobulins*** produced by the lymph nodes from the paths of the lymphatic vessels; and ***chyle*** (emulsified fats, free fatty acids and chylomicrons), which derive from the absorption of these substances from the digestive tract through the intestinal lymphatic capillaries. Daily, lymphatic vessels return approximately 40% of total plasma proteins into the circulatory system, allowing the entry of chylomicrons and immunoglobulins into circulation. Thus, the lymphatic system has both roles in homeostasis with maintaining of plasma volume and in immunity, protecting the body from the action of foreign substances and infectious agents (bacteria, viruses).

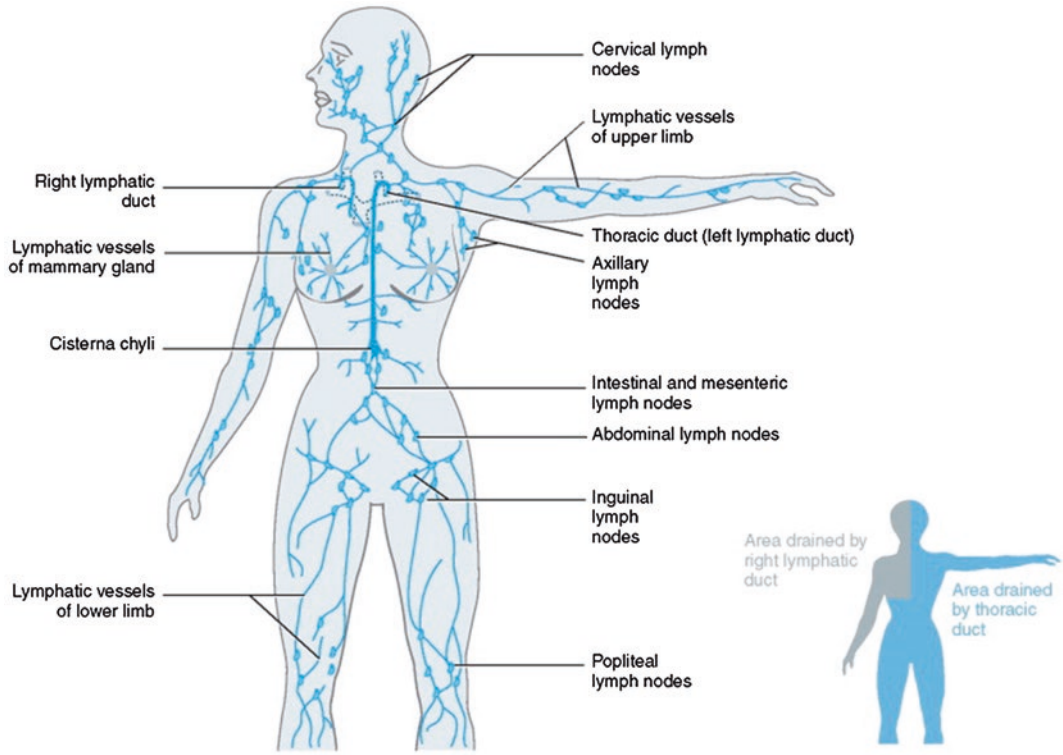

Fig. 3 Major vessels and nodes of the lymphatic system. Lymphatic vessels and lymph nodes are named according to their location in the body. Lymph collected by smaller lymphatic vessels throughout the body eventually drains into larger lymphatic vessels called the thoracic duct (left lymphatic duct) and right lymphatic duct. The cisterna chyli is the base of the thoracic duct and drains the lumbar and intestinal lymphatic regions. Lymph flows from the thoracic duct and right lymphatic duct into the left and right subclavian veins, respectively, of the heart to reenter the blood circulation. (Not all lymphatic vessels or lymph nodes are shown.) From [8] with permission

The capillary filtration process is under the action of a pressure gradient resulting from (1) capillary hydrostatic pressure (17 mmHg), (2) capillary colloidosmotic pressure (28 mmHg), (3) colloidosmotic pressure of the interstitial fluid (5 mmHg), and (4) hydrostatic pressure of the interstitial fluid. Physiologically, the last pressure component is the only variable that constantly maintains a balance at a level of 6 mmHg. Lower values, around 0 mmHg, allow for the increase of the pressure gradient between interstitium and lymphatic capillary, which leads to increased lymph flow. At hydrostatic fluid pressures greater than or equal to 1–2 mmHg, there is no increase in lymph flow, which can be explained by extrinsic compression of lymph nodes [5]. There are physiological variations in lymph flow, which consist in its decreasing during sleep and increasing throughout the day [11]. It can be said that the lymphatic system is a special segment of the circulatory system represented by the circulating fluid—lymph and the lymphatic vessels. The lymphatic system differs from the vascular system itself because it does not form a closed circuit. Lymph is transported from the lymphatic capillaries into the venous system via the lymphatic vessels.

It has to be mentioned that some authors suggested that the origin of the lymphatic system is not represented by the lymph capillaries, but it is represented by certain preformed and tubular structures, formed of non-endothelial filaments with interstitial location and which precede lymphatic capillaries [4]. These are found in all tissues but have different lengths and densities depending on the location. Thus, in the brain, these structures have long lengths, stretching long distances from the surface to the surface of the lymphatic capillaries. In the viscera, however, the length of these preformed canals is small, with a large density of lymph capillaries in the immediate vicinity. Distribution and trajectory of lymphatic lymph nodes vary according to the territory they serve. On a superficial level, the lymphatic vessels exhibit a vein-like tract, being located subcutaneously, while viscerally lymphatics are accompanying the arteries as a vascular plexus around them. Those that originate at the intestinal level leave the intestinal villi, being named lacteales [10].

Along lymphatic vessels there are 400–700 lymphatic nodes representing a filter of lymphatic circulation. The lymph nodes are oval in varying sizes (from a few mm to 1–2 cm). They are aligned along the lymphatic vessels and tend to grow in size as they approach the thoracic duct. Predominantly they have axillary, groin, and cervical localizations on the splanchnic vessels. It represents the "nucleus" of the lymphatic flow brought through afferent vessels (in large numbers) and the efferent lymphatic vessels that run off the lymph node (fewer), but have a larger caliber which makes these lymph nodes to represent the filter of the lymphatic circulation. Therefore, a number of 4–5 lymphatic vessels enters the lymph node and only the efferent lymphatic vessel carries the lymph from the lymph node. Each lymph node has a concave face where exists the lymphatic hilum through which the artery and nerve endings enter and the vein exits [4].

Structurally, lymph nodes are made up of a fibrous capsule from which fibrous trabeculae descend inwards, similar to a mesh. The interior is made up of subcapsular sinuses, communicating with lymphatic vessels and parenchyma. The ganglion parenchyma is structured in 2 parts (medulla and cortex), each part with different functions. Overall the parenchyma contains lymphatic and reticular tissue rich in lymphocytes and macrophages, organized as nodules. Each cortical node contains lymphocyte aggregates, which surround a less dense area called „germinal centre". This germinal centre represents the site of maturation of lymphocytes, which subsequently transforms into plasmocytes with a role in the formation of antibodies. Medulla is formed from sinuses and conjunctive bands. Sinuses are taped by cells capable of phagocytosis, called reticulo-endothelial cells.

The lymph flow mechanism is favored by the specific positioning of valves in the lymphatic vessels which are larger at the level of the lymph nodes. Lymphatic vessels have their own wall, similar to that of the veins, but with some particularities: thinner walls, relatively larger lumen and endothelial flaps preventing „backflow''.

Anatomy of the Lymphatic System

Cisterna Chyli

Cisterna chyli also known as receptaculum chyli, has the form of a dilated bag located at the proximal end of the thoracic duct (left lymphatic duct), in which the intestinal lymph trunks and both lumbar trunks open (Fig. 4) [12]. It is present inconstantly (in 25–50% of cases is missing), and when it is retroperitoneal is located between the inferior vena cava and the aorta, on the anterior side of the lumbar vertebrae L1 and L2, having a length of 3–4 cm and a width of 2–3 cm [6, 13, 14]. The lymphatic area drained by the cisterna chyli is represented by the lower part of the body and the abdominal viscera.

Lumbar lymphatic trunks drain the lymph of the lower limbs, the pelvis, the kidneys and the adrenal glands and a large part of the deep lymphatic abdominal wall. Both are located between the lumbar vertebral bodies and the inferior vena cava (right) and the aorta (left), at the upper pole of the lumbar lymph chain.

The lymphatic intestinal trunk drains lymph from the over- and below-mesocolon (the pancreas, the spleen, the lower and front part of the liver), with the exception of the postero-upper portion of the liver.

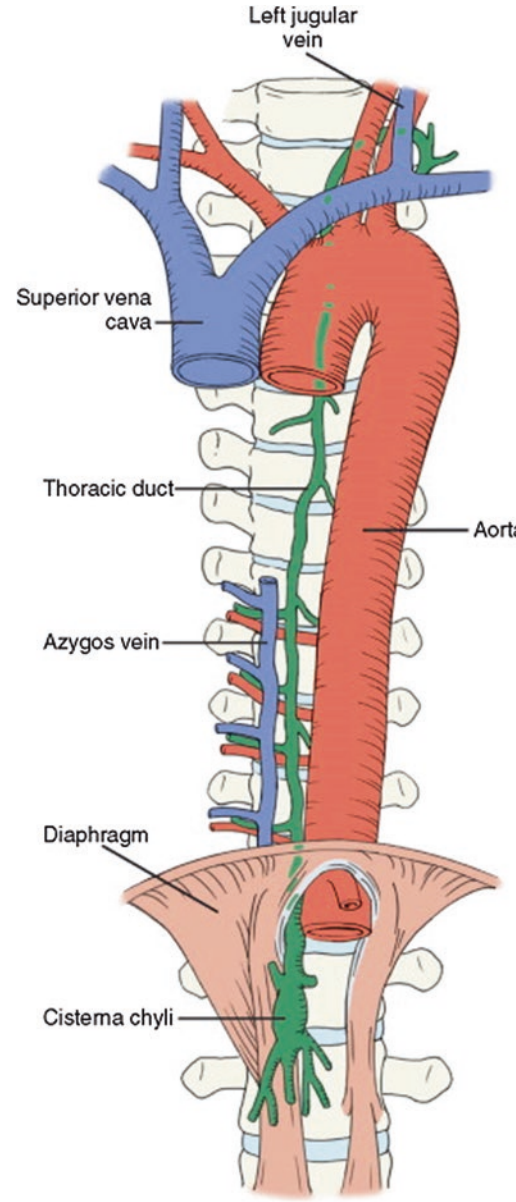

Fig. 4 Anatomy of the thoracic duct. From [12] with permission

Thoracic Duct

Because the lymph in the body is mainly drained by the thoracic duct (left lymphatic duct), this represents the main collector of the lymphatic system (Fig. 4) [12].

Origin, Trajectory, Relationships

From a topographic viewpoint, the thoracic duct is positioned between the aorta, esophagus and the azygos vein. The thoracic duct originates at the level of the cisterna chyli (vertebrae L1–L2) and reaches the base of the neck. The length of the thoracic duct is 38–45 cm. Start in the abdomen at the upper pole of the cisterna chyli, between the inferior vena cava and the aorta, near the right crus of the diaphragm. It presents a sinuous route, explained by its embryological development [6, 13, 14]. In the first portion it rises from the abdomen into the chest. It crosses the diaphragm through aortic hiatus, where the posterior aorta is located. Subsequently, the ascending route continues, the thoracic duct being located intrathoracic

but outside of pleura, in the visceral compartment of the mediastinum, ascending before the right edge of the vertebral bodies, posterior of the esophagus, and between the aorta and the azygos vein, and anterior to the intercostal arteries.

The posterior relations of thoracic duct at this level are: the thoracic spine, the right intercostal arteries and the terminal portions of the hemiazygos veins. The anterior relations are diaphragm, esophagus and pericardium. This trajectory at the right of the median line ends at the thoracic vertebra T5–T6, where the thoracic duct changes its direction passing to the left and posterior of the esophagus, reaching the upper part of the visceral mediastinum.

Further, thoracic duct ascends behind the aortic arch and the origin of the left subclavian artery, having the esophagus to the right and the mediastinal plexus to the left. At this level, the thoracic duct was identified extrapleural, on the left side of the esophagus, most commonly in the Poirier's triangle (comprised between the lower aortic arch, the left subclavian artery and spine) (in 45.7% of the cases) or between the common carotid artery and the left subclavian artery (in 28.6% of cases) [15].

Due to close relationships with the aorta, esophagus and heart, any surgery or trauma of these organs can lead to the injury of thoracic duct. This is most commonly found in esophageal resections for esophageal cancer.

The thoracic duct continues its ascending path, passing through the upper thoracic aperture, reaching the cervical region, where it flows to the confluence or junction between the left internal jugular vein and the left subclavian vein. At this level, the thoracic duct presents as an arch with antero-inferior concavity at 2–4 cm above the clavicle, having important vascular relations with:

- Anterior: left common carotid artery, left internal jugular vein;
- Posterior: Left subclavian artery, vertebral artery and vertebral vein, and thyrocervical trunk that divides into next branches: inferior thyroid, suprascapular, transverse cervical and ascending cervical arteries.

During surgical dissection, for the discovery of the thoracic duct, it is also necessary to consider relationships with nerve structures such as vagus nerve (anterior) and phrenic nerve (posterior) in order to avoid their injury.

If the cisterna chyli has a diameter of about 2 cm, the thoracic duct that is representing its cranial extension has a smaller diameter (2–3 mm). The thoracic duct reduces considerable its diameter to the middle of the chest, then expands again before it spills or empties into the subclavian-jugular venous junction.

The general appearance of the thoracic duct is varicose because of its flexibility and periodic contractions, and on the other hand, its tendency to divide into branches that later are joining into a plexiform network.

The thoracic duct exhibits both anastomoses with the right lymphatic duct, and lymphatic-venous shunts, which can function in bidirectional way depending on the pressure of vein system or lymphatic system. They perform the role of a valve for the larger pressures, preventing the raising of pressure in lymphatic vessels or venules [10].

The thoracic duct has about 22 valves [5], including 4–5 at the abdominal level, 5–6 at thoracic level between the diaphragm and the aortic cross, and 11–13 in thoracic area above the aortic cross and the cervical region. The increased density of the valves in the terminal portion of the thoracic duct can be explained by the need to subdivide the lymphatic column into the proximity of a high pressure predisposing regime at the jugular-subclavian junction [16].

The thoracic duct receives nerves from the sympathetic chain and the vagus nerve [13, 14].

Anatomical Variants of Thoracic Duct Spillage

A characteristic feature of the thoracic duct is the variety of spillage types (over 35%). Of the most common variants encountered, we mention (Fig. 5) [6, 7, 11, 17–21]:

- Double thoracic duct with left spill or even plexiform;

- Thoracic duct that ends in the right jugulo-subclavian venous junction—in the absence of the left thoracic duct (the existence of a right thoracic duct as the major lymph circulatory function was cited);
- Thoracic duct in "Y" with bilateral ending or spill, in which the left branch flows in the classical way, and the right one at the level of the right jugulo-subclavian junction;
- Double thoracic duct with bilateral spillage;
- Thoracic duct with endding or spill in the azygos vein;
- Thoracic duct with spillage in the hemiazygos vein;
- Thoracic duct with end in the left subclavian vein;
- Thoracic duct spilling into the vertebral vein;
- Thoracic duct with endding in the left brachiocephalic vein.

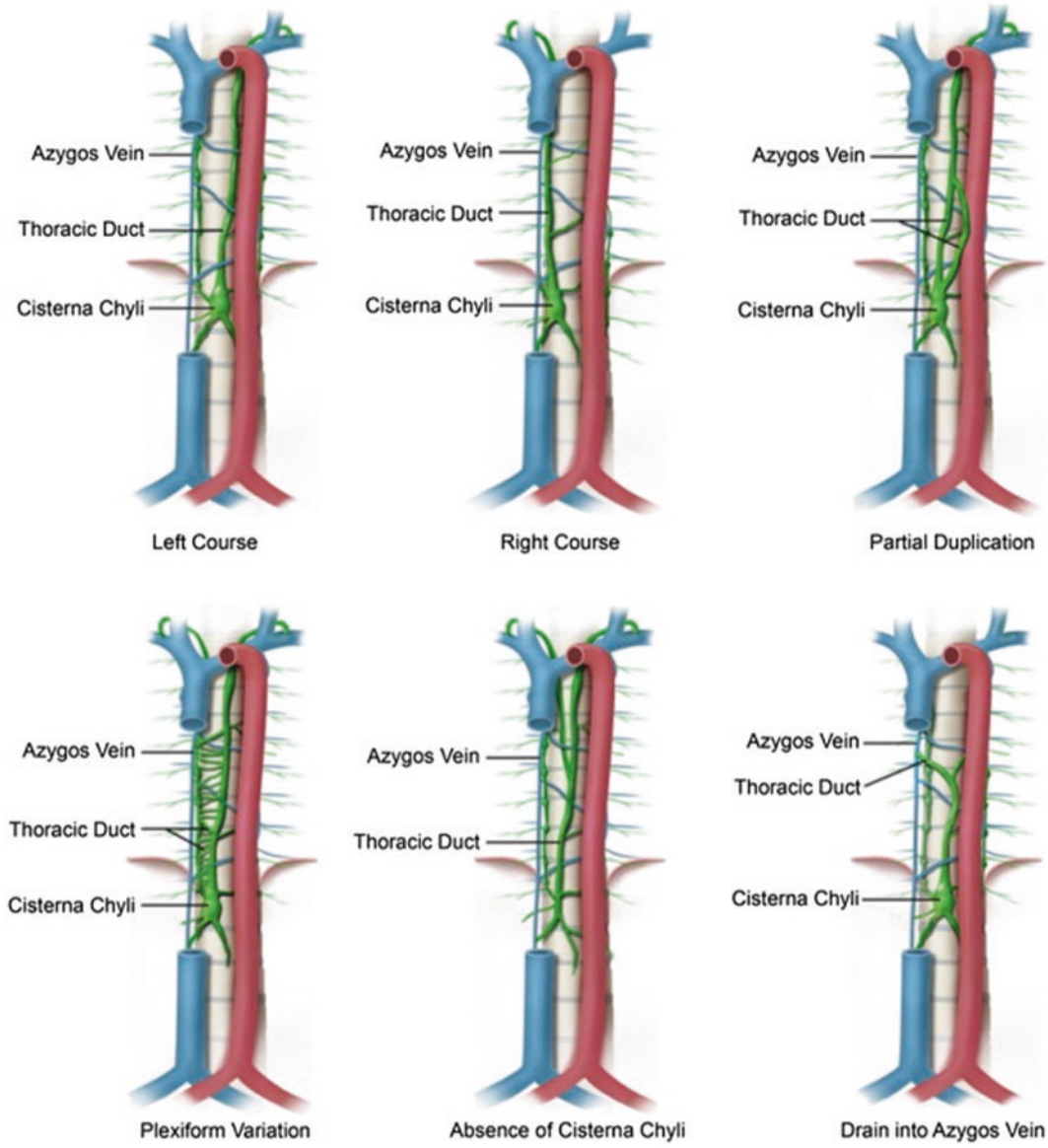

Fig. 5 Anatomical variants of origin, path and endding of the thoracic duct. From [21] with permission

Thoracic Ducts Tributaries

The thoracic duct tributaries are:

- A descending branch from the lateral intercostal lymph nodes of the last 6–7 intercostal spaces—opens in the proximal portion of the thoracic duct on either side;
- Another trunk that drains the lymph from the upper lumbar nodes passes through the diaphragmatic pillar, reaching the chest cavity and spilling into the thoracic duct from one side to the other;
- Left jugular trunk and left subclavian trunk drain lymph from the cervical region;
- Another trunk, the left broncho-mediastinal can drain in the thoracic duct at the cervical region but more frequently opens in the left jugulo-subclavian venous confluence.

In the thoracic portion there are direct lymphatic tributaries that flow into the thoracic duct. Of these, the most common are from the following lymph nodes [22, 23]:

- Tracheobronchial,
- Mediastinal (anterolateral and posterior),
- Posterior intercostals of the first six left intercostal spaces.

Right Lymphatic Duct

It is a stand-alone structure with a length of 1–2 cm (Fig. 3) [8]. Sometimes it is the right branch of the thoracic duct itself the bilateral variant of spillage.

The right thoracic duct is in the right posterior mediastinum, climbs into the cervical region along the medial edge of the anterior scalen muscle and flows into the jugulo-subclavian venous confluence.

The areas drained by the right duct are as follows:

- The right side of the head and the cervical region;
- Upper right member;
- Right thoracic wall;
- Right lung;
- The right side of the heart;
- The convex surface of the liver.

As with the thoracic duct, the lymphatic drainage of right duct has two semilunar valves that play a role in unidirectional lymph drainage.

There are 3 terminal collector trunks of the right lymphatic duct:

- The right jugular trunk—drains the right craniocervical side;
- The right subclavian trunk—collects lymph from the upper right member;
- The right bronchomediastinal trunk—gather lymph from the rest of the above-mentioned territories.

The collector trunks have 3 variants of spillage:

- All three lymph trunks are ending separately into the right jugulo-subclavian junction—the most common condition;
- A right lymphatic trunk is formed by joining the right jugular and the right subclavian trunks, the last trunk having a separate spill;
- All three main trunks join together, forming the lymphatic duct as a proper one.

Self-study

1. Which statement is true:
   a. The lymphatic system originates from the lateral mesoderm at the end of the fifth week of embryonic development
   b. The thoracic duct is also named left lymphatic duct or Van Hoorne's canal.
   c. The lymph capillary wall consists of a single layer of endothelial cells, thinner and more flattened than those present in blood capillaries; with basal membrane
   d. The thoracic duct transports up to 4 L of lymph per day.
2. Which statements are true:
   a. In 45.7% of the cases, Poirier's triangle is comprised between the lower aortic arch, the left subclavian artery and spine.

b. In 28.6% of cases, Poirier's triangle is comprised between the common carotid artery and the left subclavian artery.
c. Injury of thoracic duct is most commonly found in esophageal resections for esophageal cancer.
d. Thoracic duct can end into the left subclavian vein.

Answers

1. Which statements is/are true:
   a. CORRECT.
   b. CORRECT
   c. NOT CORRECT
   d. CORRECT
2. Which statements are true:
   a. CORRECT
   b. CORRECT
   c. CORRECT
   d. CORRECT

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Embryology and Surgical Anatomy of the Mediastinal Lymph Nodes

Jon A. Lutz

Key Points

- The mediastinum is a crossroads of different organ systems in the thoracic cavity
- The mediastinal lymph nodes develop from the paratracheal and internal thoracic lymph plexus arising around the 5th to 6th week of embryogenesis
- To simplify the understanding of its anatomy, the mediastinum is divided in compartments (superior and inferior, anterior, middle and posterior)
- The IASLC has agreed on a mapping of the mediastinal lymph nodes, which is of uttermost importance in thoracic oncology.

Introduction

The embryology of the mediastinum and its lymphatic system is a subject of only few articles or textbooks and even more seldom their main topic. The known developmental steps will be highlighted in this chapter. There are different approaches to the complex anatomy of the mediastinum. Arbitrary, the mediastinum has been divided in compartments in a craniocaudal or ventrodorsal way. This manner can be suitable from a radiological point of view. For surgical purpose—and especially for thoracic oncology—the orientation in relationship to the main anatomic structures of the mediastinum is more appropriate and is essential to understand the mapping of the mediastinal lymph node stations.

Embryology

In the 3rd week of embryogenesis, the bilaminar embryonic disc becomes trilaminar in a process called gastrulation [1]. Some cells move to the cranial lateral plate to form the cardiogenic mesoderm, where the primitive heart will arise as endocardial tubes.

During the 4th week, there is a rapid flexion in the craniocaudal axis of the embryo and a folding of the lateral plate forming a tunnel. The tubular heart eventually starts to beat at this stage and the respiratory diverticulum—giving rise to the trachea and lungs—appears ventrally on the foregut endoderm.

During the 5th and 6th week, the borders of the mediastinum become more defined. The primary bronchi give rise to three secondary bronchi on the right and two on the left side, corresponding to the future lung lobes. The pleuropericardial folds grow between the

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developing heart and lungs, forming the lateral limits of the mediastinum. The spine (dorsal edge) appears in form of vertebral precartilage, followed by the ribs and sternal mesenchymal arches (ventral). Caudally the future mediastinum is boarded by the septum transversum, primordia of the diaphragm.

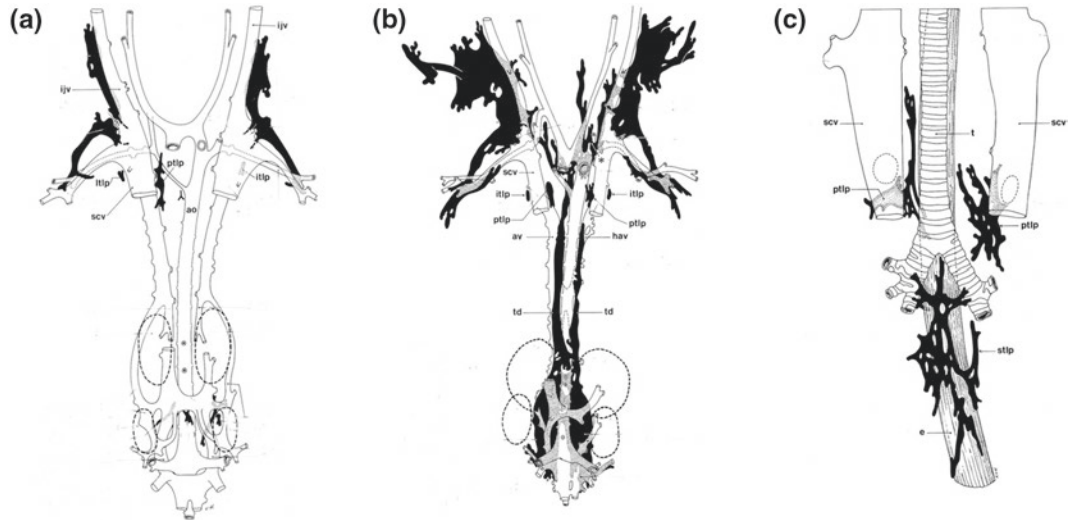
Lymphatic primordia appear in the mediastinum during the 6th week [2]. The paratracheal and the internal thoracic lymph plexuses develop and fuse with other plexuses, especially the mesenteric lymph plexus, giving rise to the thoracic duct (Fig. 1a and b). In the 8th week, the subtracheal lymph plexus with its relationship to the trachea and esophagus becomes also visible (Fig. 1c).

Surgical Anatomy

(a) Compartments of the mediastinum

The complex anatomy of the mediastinum has led to a division of this entity into compartments. From a radiological point of view the upper and lower mediastinum are often separated at the height of the junction of the manubrium-body of the sternum [3]. The inferior part is then further divided into anterior, middle and posterior compartments (Fig. 2, upper illustration). The anterior mediastinum includes heterogeneous structures like the ascending aorta, the superior vena cava and the thymus gland, all situated between the posterior border of the sternum and the ventral pericardium. The posterior mediastinum contains the esophagus, the descending aorta, the sympathetic chain and the thoracic duct. It lies posteriorly to the pericardium and is boarded dorsally by the paravertebral portions of the ribs. The middle compartment is situated in between and includes the trachea and the heart, including most of the great vessels.

This division of the mediastinum is somewhat arbitrary and not unique, leading to confusion in the localization for example of mediastinal tumors [4]. From a surgical point of view, another compartmentalization is more pragmatic (Fig. 2, lower left illustration). It divides the anatomic mediastinum in an anterior



(ijv = internal jugular vein, itlp = internal thoracic lymph plexus, scv =superior vena cava, ptlp = paratracheal lymph plexus, ao = aorta, av = azygos vein, hav = hemiazygos vein, td = thoracic duct, stlp = subcarinal plexus, e = esophagus)

Fig. 1 **a** Lymphatic primordia in the mediastinal region, week 6: paratracheal and internal thoracic lymph plexuses. **b** Fusion of the lymph plexuses forming the thoracic duct. **c** Apparition of the subcarinal lymph plexus and its relationship to the trachea and esophagus, week 8

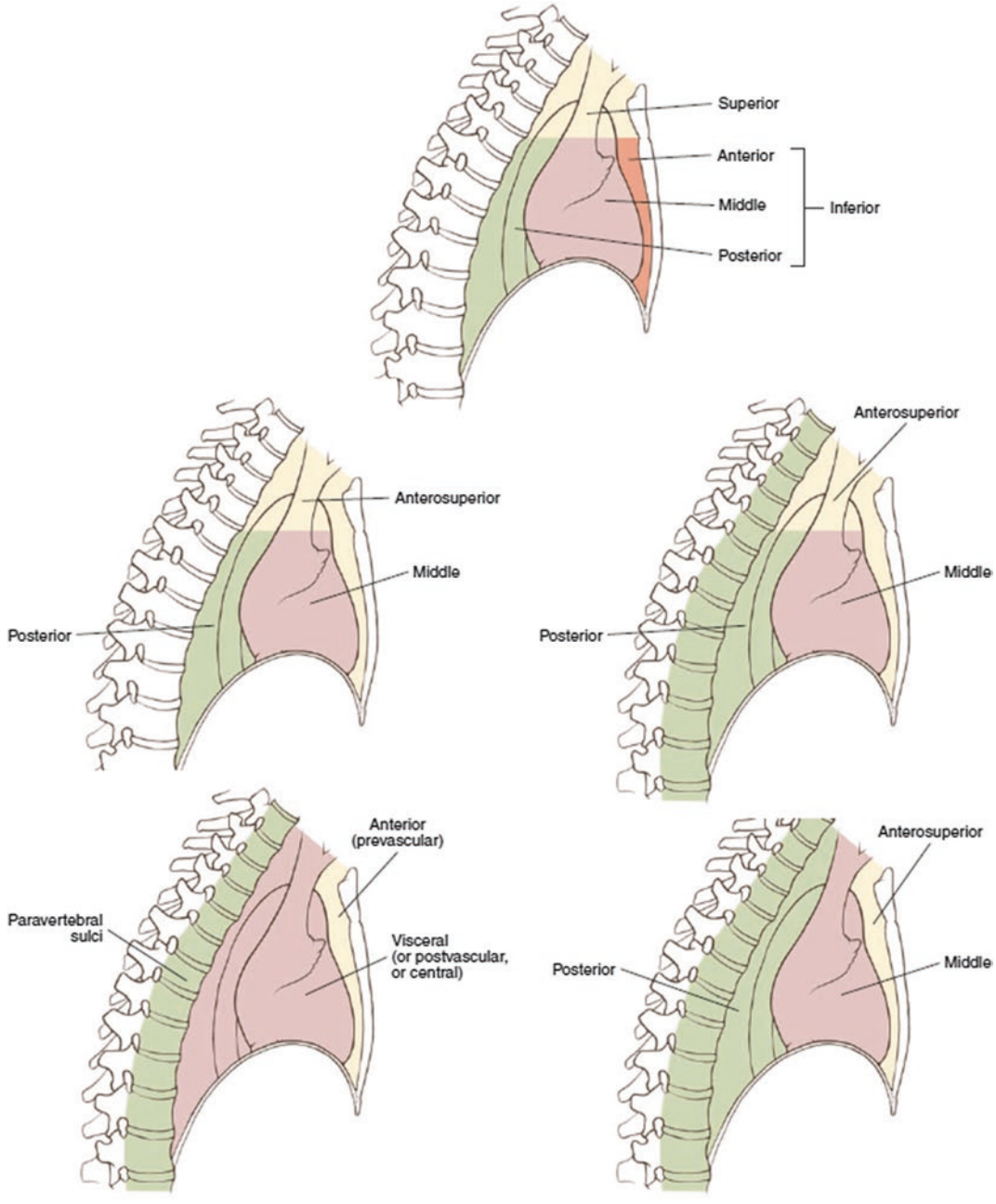


Fig. 2 Different examples of dividing the mediastinum in compartments

and visceral compartment, leaving the paravertebral sulci as the origin of posterior mediastinal tumors [5].

(b) Zones of the mediastinal lymph nodes

From a historical point of view, the study of the lymphatic system started quite late and this is

even more the case for the mediastinal lymphatics. Nohl-Oser has written an excellent synthesis of this evolution in his introduction [6]. In the same publication, he analyses the ipsi- or contralateral mediastinal spread of lymphatic metastasis for left or ride sided malignant lung tumors, using mediastinoscopy and a systematic grouping of lymph nodes. The first modern and widely applied mapping of the mediastinal lymph nodes is due to Naruke [7]. However, the American Thoracic Society (ATS) proceeded to a refining of the anatomical landmarks in the 1980s, which was further modified by Mountain and Dressler [8], leading to the coexistence of competing consensus on mediastinal staging in North America and Japan, including Europe. The International Association for the Study of Lung Cancer (IASLC) created the Lung Cancer Staging Project in 1998. This resulted in the development of an international database, which was the groundwork for highlighting the discrepancies in nodal staging between the Naruke and the modified ATS mediastinal lymph node maps [9], the best example being subcarinal lymph nodes classified either as level 7 or 10. This collaboration finally produced a widely accepted map with clear mediastinal lymph node zones, as well from a radiological as from a surgical point of view (Fig. 3, Table 1).

(c) Lymphatic spread to the mediastinal lymph nodes

The lung has two lymphatic drainage pathways, a visceral pleural network and a parenchymatous peribronchovascular plexus [10]. The visceral pleural network covers the lung surface and its collectors drain the lymphatic fluid in direction of the hilum. They either anastomose with the peribronchovascular plexus or drain directly in the mediastinum. The peribronchovascular plexus follows the bronchial tree on the same path but in an opposite direction to the bronchial arteries. In the hilum, they join either the ipsilateral or the contralateral mediastinal lymphatics. The connection to the venous system at the left internal jugulosubclavian angle can be over direct pathways or through the thoracic duct. Some of the lymphatic vessels of the lower lobes drain within the pulmonary ligament and eventually join lymph node stations below the diaphragm [11].

Lobe specific lymphatic drainage has been studied in various cadaveric [12] studies and correlated to clinical findings in patients operated for bronchial carcinoma [13]. Watanabe examined 139 patients with pN2 non-small cell lung cancer (NSCLC) in the lower lobe [14]. He looked for a difference in pattern of mediastinal lymph node metastasis between patients with tumors in the superior or basal lower lobe. In patients with superior mediastinal involvement (stations 2–4), he found a higher prevalence of synchronous metastasis to the subcarinal nodes (station 7) in tumors of the basal segments, suggesting a direct pathway from the superior segment of the lower lobe to the superior mediastinum. Those findings could not be confirmed in a further study by Zomizawa [15]. Interestingly, despite differences in pattern of mediastinal lymph node metastasis, both studies showed the same advantage in disease free survival for NSCLC located in the basilar segments. This lead to the concept of lobe specific lymphadenectomy, which was explored in a large retrospective study with promising results [16]. However, it has to be underlined that this approach has not yet reached the level of evidence to be considered as standard practice.

(d) Topography of the mediastinal part of the recurrent laryngeal nerves

During mediastinal lymphadenectomy or mediastinoscopy, one should be particularly aware of the potential risk to harm the recurrent laryngeal nerves [17]. The topography of the left recurrent laryngeal nerve as it turns around the aortic arch is well known, particularly because the left vagal nerve is nearly always visible on this part of its course. On should be therefore be very careful during clearance of lymph node stations 5 and 6. The risk to harm the left recurrent laryngeal nerve during mediastinoscopy is less familiar. Not only thermal injury in the left

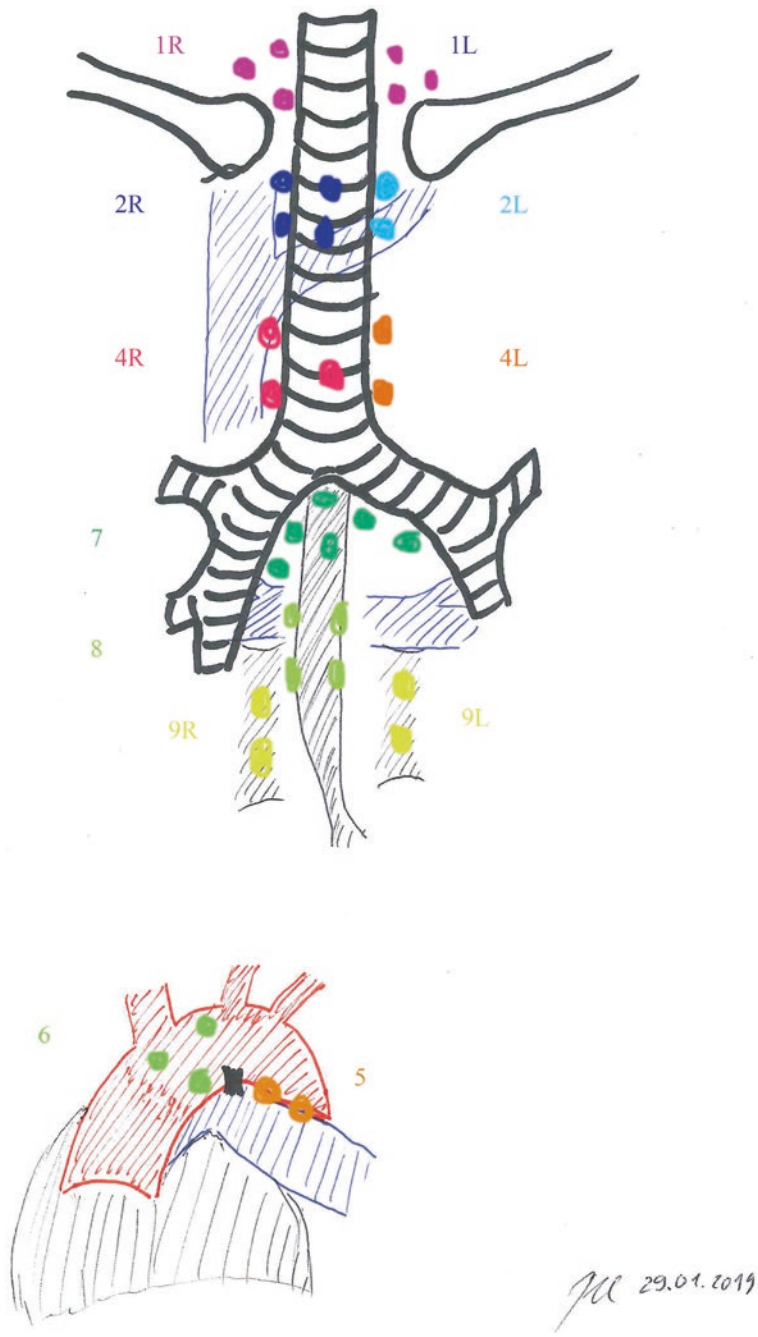


Fig. 3 Mediastinal lymph node map following recommendations of IASLC [9]

lower paratracheal region (station 4L) can be deleterious, but also simple excessive traction on the nerve through indirect forces in the lower pretracheal space behind the aorta can induce damage [18]. On the right side, the recurrent laryngeal nerve has a much shorter intrathoracic course. It turns around the right subclavian artery, which height can vary from the level of T1 to T3, yet one should keep in mind that moderate traction on the right vagus nerve can displace the origin of the recurrent nerve as much as 14.8 mm [19].

Table 1 IASLC mediastinal lymph node map (modified from [9])

Station/name	Upper border	Lower border	Right/left or AP	Zone and N-stage[a]
#1 Supraclavicular	Cricoid	Clavicles	Midline	Supraclavicular N3
#2 Upper paratracheal	Lung apex	Innominate vein	Left border of trachea	Superior mediastinal N2
#3a Prevascular	Chest apex	Carina	Sternum/superior vena cava	Superior mediastinal N2
#3p Retrotracheal	Chest apex	Carina	Trachea/ spine	Superior mediastinal N2
#4 Lower paratracheal	Innominate vein/aortic arch	Azygos vein/main PA	Left border of trachea	Superior mediastinal N2
#5 Aortopulmonary	Aortic arch	Main PA	Lateral to LA	Aortic nodes N2
#6 Paraaortic	Aortic arch	Aortic arch		Aortic nodes N2
#7 Subcarinal	Carina	IB/LLB		Inferior mediastinal N2
#8 Paraesophageal	IB/LLB	Diaphragm	Midline	Inferior mediastinal N2
#9 Pulmonary ligament	Inferior PV	Diaphragm		Inferior mediastinal N2

[a]If ipsilateral tumor, *AP* anterior/posterior, *PA* pulmonary artery, *LA* ligamentum arteriosum, *IB* intermediate bronchus, *LLB* left lower bronchus, *PV* pulmonary vein

Conclusion/Summary

Knowing the embryology of the mediastinal lymphatic system can help understand the variety and the inconstancy of patterns of mediastinal spreading of metastasis from lung tumors. The IASLC lymph node map is well established and their recommendations should be applied in thoracic oncologic surgery. The topography of the recurrent laryngeal nerve should be a basic knowledge when performing mediastinal lymphadenectomy.

Self Study

(1)Which mediastinal lymph node metastasis of a left lower lung NSCLC is N2?
   a. Station 5
   b. Station 7
   c. Pretracheal lymph node on the height of azygos vein
   d. Left side of trachea above manubrium.

(2)Which nodal station is particularly at risk for lesion of the laryngeal recurrent nerve?
   a. Station 4R
   b. Station 2R
   c. Station 6
   d. Station 8.

Answers

(1)Which mediastinal lymph node metastasis of a left lower lung NSCLC is N2?
   a. Station 5—CORRECT!
   b. Station 7—CORRECT!
   c. Pretracheal lymph node on the height of azygos vein—N3!
   d. Left side of trachea above manubrium—N3!

(2)Which nodal station is particularly at risk for lesion of the laryngeal recurrent nerve?
   a. Station 4R
   b. Station 2R—CORRECT!
   c. Station 6—CORRECT!
   d. Station 8.

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Surgical Approaches and Operative Techniques for the Mediastinal Lymphatic System

Claudiu E. Nistor, Adrian Ciuche, and Ecaterina Bontaș

Key Points

- The thoracic duct injuries can occur at any anatomical level.
- Failure to recognize this complication at the right time of surgery or after a trauma, could have serious consequences.
- Thoracoscopic minimally invasive techniques can be applied to traumatic thoracic canal lesions in the thoracic region.

Introduction

The thoracic duct injuries can occur at any anatomical level depending on the etiology which cause the developping of chylous fistula. Due to close relationships with the aorta, esophagus and heart, any surgery or trauma of these organs can lead to the injury of thoracic duct (Fig. 1) [1]. At the level of mediastinum, injury of the thoracic duct may cause cervical chylous fistula, chylothorax, chylomediastinum, chylopericardium, followed by hypovolemia, coagulopathy, hypoalbunemia, immunosupression or decreased immunoglobulins, low enzymes, electrolyte disturbances, even malnutrition with high morbidity. Not the lesion itself, but the failure to recognize this complication at the right time of surgery or after a trauma, could have serious consequences, taking into account the lymph flow that is about 2–4 l/day [2]. In most cases, it is known that the length of hospitalization is long, with slow recovery, because is difficult to manage treatment due to associated loss of electrolytes, proteins, and lipids. Treatment should take into account both the triggering cause and the extent of lymphatic leakage. First approach in the case of chylous fistula of the thoracic duct is conservative treatment. But surgery is an option too. This chapter underlines basic surgical knowledge about injury of the thoracic duct in mediastinum.

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Cervical Thoracic Duct Fistula (Cervical Chylous Fistulae, Cervical Chyle Leak)

It is a rare complication of 1–3%, being more common in the left side of the throat (75%)

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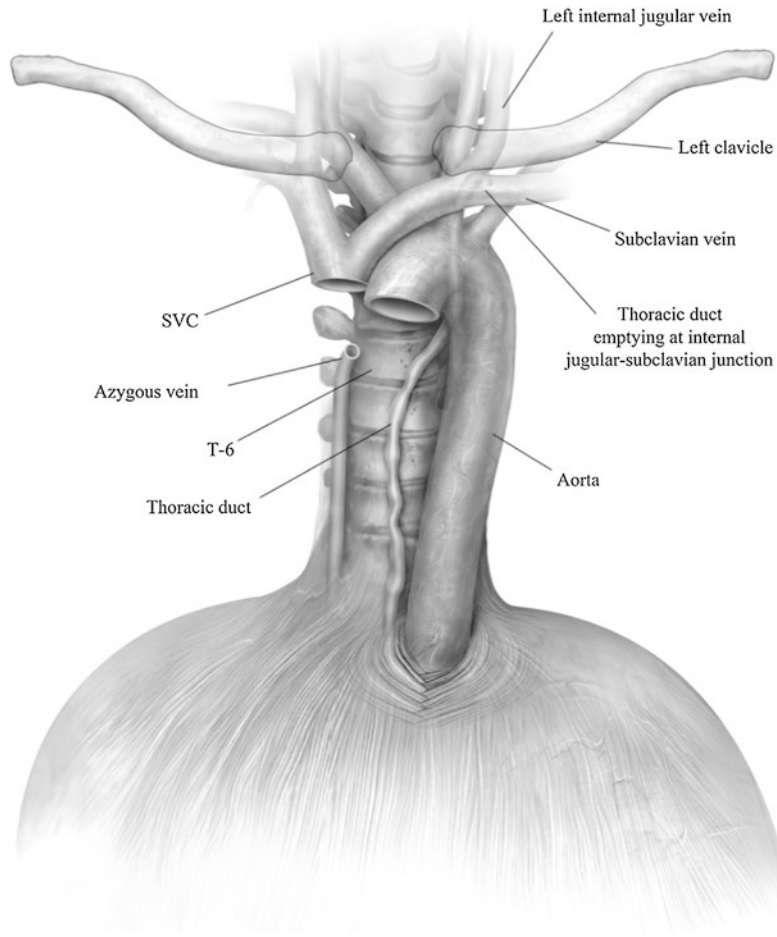

Fig. 1 Thoracic duct anatomy. SVC = superior vena cava. From [1] with **permission**

than in the right (25%), which occurs more frequently after surgery of the cervical region such as radical dissection of the throat, ganglion biopsy, cervical ribs resection, or thyroidectomy [3]. Central venous cannula and penetrating cervical trauma are other causes of generating cervical chyle fistula.

Taking into account the etiology of cervical chyle fistula, the principles of treatment are based on:

- cervical wound management;
- lymphatic flow monitoring.

The treatment of the cervical chyle fistula contains three stages: conservative, hormonal, surgical [4].

Conservative Treatment

The first therapeutic gesture is complete exclusion of oral nutrition and the introducing of parenteral nutrition with the aim to avoid nutritional loss. Sometimes, when lymphatic drainage by fistula is small, a high protein diet rich in medium chain triglycerides [5–7] can be established because their direct absorption into the blood (portal circulation) at the intestinal level does not participate in the production of chyle. This restrictive feeding method allows to reduce lymph flow in the cervical chylous fistula.

Overall, the lymph flow rate is increased by coughing or straining, fatty meal, intestinal peristaltis, and movement of the torso or upper extremities [8–10]. Therefore, next therapeutic step is decreasing the fat content in the diet

that leads to the reduction of lymph flow and consequently to the reduction of the lymph loss through the chylous fistula. The oral diet without lipids can be considered in case of quantitative reduced lymphorrhea.

Total physical rest is required because muscle activity is an important lymphokinetic factor, and as a consequence, a normal respiratory cycle does not increase lymph flow in the thoracic duct and, implicitly, neither in the fistula.

Surgical Treatment

Until 1900, standard treatment of cervical chylous fistula was the compression of the supraclavicular fossa with compressive bandages. Surgical ligation of the thoracic duct was considered a treatment method with a high mortality rate of over 12.5% [2]. Subsequently, the ligation of the thoracic duct at the cervical level has been shown to be an effective surgical treatment option with low mortality [11, 12]. In surgical practice, we can deal with two situations, depending on the intrapostoperative or postoperative recognition of the thoracic duct damage or leak. Currently, the thoracic duct ligation is the main option in patients requiring surgical treatment.

Intraoperative Lesion Recognition

Generally, any abdominal, thoracic or cervical surgery with the risk of interfering the thoracic duct should be preceded by 2–3 hours before surgery, by the administration of 100–150 ml of cream for intraoperative highlighting of dilated thoracic duct; and if it is damaged, for recognition of the chylous leak. If there is intraoperative suspicion of a thoracic duct damage, it is imperative to carefully examine the wound. Identification of the lesion is facilitated by placing the patient in the Trendelenburg position and administering of a positive pressure ventilation by the anesthesiologist, all these maneuvers increase the lymph flow. If the thoracic duct lesion is recognized, the thoracic duct must be isolated with ligation (Fig. 2) [13]. If not possible, a ligation involving the neighboring tissues can be made, avoiding damage to vascular structures.

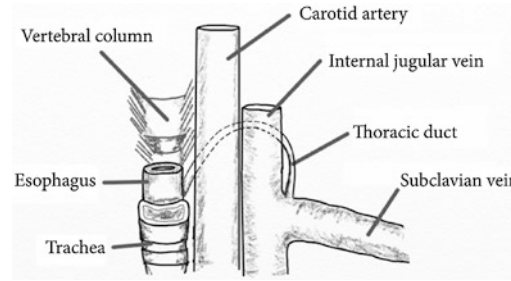

Fig. 2 Cervical course of the thoracic duct. The thoracic duct enters the neck lateral to the esophagus, ascending superiorly and laterally behind to the carotid and internal jugular vein before turning inferiorly and anteriorly to join the venous circulation at the confluence of the internal jugular vein and subclavian vein. From [13].

Postoperative Lesion Recognition (Reoperation)

Typically, intraoperative thoracic duct lesion unidentified during cervical surgeries (Daniels lymph node biopsies, laryngectomy, etc.) [14–19], is manifested by prolonged and rich chylous drainage, or by the appearance of respiratory disturbances when the chylothorax occurs. Once the diagnosis is established by analyzing the fluid on the drain tube or by thoracentesis, the time of the surgical intervention will be decided according to the nutritional and functional status of the patient. ***Reoperation*** is indicated when the fistula has a flow rate greater than 500 mL/day for more than 4 days and in patients whose nutritional and/or functional status progressively degrades.

The thoracic duct leak or lesion can be identified by administering cream or olive oil (approximately 100–200 ml) with 2–3 hours before reoperation and even intraoperatively on the naso-gastric tube. For the avoidance of postoperative Mendelson syndrome, it is necessary to further suck the fat content of the stomach. Another much faster method of identifying the thoracic duct lesion during surgery is to inject the 1% Evans blue solution at the level of leg. As such, the leak is difficult to visualize due to dye impregnation of the tissues adjacent to

the fistula, which is a major drawback of this method [20].

Once the thoracic duct lesion has been identified, direct double ligation is essential for stopping loss of the lymph and for avoiding the patient's hemodynamic and nutritional impairment.

The use of tetracycline in the wound bed has been suggested by some authors for the purpose of closing the fistula by causing a local sclerosis process. This method has been applied to selected patients to avoid reoperation. The advantage of this method was to shorten the period of hospitalization [21].

It has been published that the local application of various synthetic materials such as Surgicel, with or without the use of tetracycline, TachoSil, Fibrin Glue, gel-foam, is used to facilitate the closure of the fistula [22].

The supradiaphragmatic ligation of the thoracic duct by postero-lateral thoracotomy through the right intercostal space 7 can be applied as the last solution for uncontrolled cervical fistula [20].

When a cervical chylous fistula is associated with the occurrence of the chylothorax, the latter should be treated by performing a minimal pleurectomy with careful monitoring of the lymphatic lesions based on which the subsequent therapeutic attitude will be decided.

Other types of surgeries outside the thoracic duct ligation have been experimented with the same purpose of solving chylous fistula:

- reimplantion of the duct into one of the branches of the Pirrogoff's venous junction;
- covering the leak of the thoracic duct with the application of a venous patch;
- plumbing with the flap of scalene muscles in the area of thoracic duct lesion;
- execution of a venous-thoracic duct anastomoses.

These techniques have been abandoned, double thoracic duct ligation being the only viable solution proven over time.

It should be noted that for the purpose of facilitating the identification of the thoracic duct fistula, preoperative and/or intraoperative preparation is similar to intrathoracic or intra-abdominal localizations.

Chylothorax

Conservative Treatment

Follows the same major principles as the case of cervical thoracic fistula: reduction of lymph flow through hygienic-dietary measures, excluding oral (total fasting) or the oral intake of medium chain triglycerides, with total parenteral nutrition support (TPN) and physical rest [23].

Some authors believe that about 50% of the thoracic duct fistulas are spontaneously closed or sealed with conservative treatment [20].

It is compulsory to apply parenteral nutrition to avoid hydroelectrolytic, immune and nutritional imbalances which can sometimes even lead to death [24].

It should be noted that there are controversy regarding the duration of treatment for both either child or adult. Most authors believe that this treatment, as a single attitude, should not exceed 14 days [20, 25].

Water, through the interstitial filtration process, participates in lymph formation. Therefore oral restriction should also be a fluid one, and in order to maintain the body's water balance, parenteral solutions will be used taking into account both the lymph loss and the daily requirement of the patient for water. From the point of view of electrolytes, their balance will be monitored, with the point view that the serum potassium level does not reflect the amount of potassium in the blood only after a major intracellular depletion. Therefore rebalancing must be done by assessing total hydroelectrolytic losses.

Metabolic support through intravenous nutritional products (TPN) should be take into account daily caloric losses and needs; various lipid derivatives (Intralipid) may be used to avoid major nutritional imbalances. Albumin solutions may be administered to maintain protein synthesis or to correct hypoalbunemia [23].

Specific Conservative Treatment

In cases of non-traumatic chylotorax, treatment of the cause of lymphorrhea can lead to the improvement of lymphatic losses but with a limited success rate:

- chemotherapy and irradiation in malign processes;
- anti-inflammatory treatment in sarcoidosis;
- ACE inhibitors, ARBs, beta blockers and diuretic treatment in heart failure;
- TIPS treatment (transjugular intrahepatic portosystemic shunt) in liver cirrhosis [26].

Hormonal Treatment

It has been suggested by some authors to use somatostatin or to control the production of chyle by using hormons [27]. It is assumed that hormonal use leads to a significant decrease in lymph flow to half in the day 3 after administration, and even to stop the lymph flow on day 5.

In patients with chylothorax, the use of lymphokinetic substances with effect on the intrinsic muscles of the thoracic duct (such as serotonin, prostaglandin, histamine, dopamine, acetylcholine) should be avoided. However, there are substances that can lead to decreased lymph flow, such as adenosine phosphate, that is a platelet aggregation factor with relaxing effect on lymphatic smooth muscle [28].

The treatment with somatostatin/octreotide can be given intravenously or subcutaneously, the dose being variable depending on age and weight. For the adults, there were authors who administered doses of octreotide 100–150 microg subcutaneous 4 times per day [29] or 50–200 micrograms octreotide three times daily subcutaneously [30].

In addition to somatostatin, it is also possible to try etilefrine, an alpha and beta-sympathomimetic substance, which has been used in the conservative treatment of the fistulae. The therapeutic principle is based on the spastic effects that etilefrine has on smooth muscles of the wall structure of the thoracic duct and the lymphatic system respectively. Reducing of lymphatics diameter is considered the main way to lower lymph flow [31]. Etilefrine is given as a continuous intravenous infusion at doses of 4–5 mg/hour for 7 days. The dose will be reduced in case of hypertensive and cardiac arrhythmias.

Alternative Treatment by Interventional Radiology

In highly specialized centers, the technique of cannulation and embolization of the thoracic duct has grown as an alternative method of conservative treatment, following the technique described by Cope et al. [32]. The basis of this technique is to identify the chylous fistula and the place of thoracic duct damage by lymphangiography.

It is preferred the cannulation and embolization of the thoracic duct as an interventional treatment method. In situations where the thoracic duct can not be cannulated, percutaneous needle disruption of lymphatic pathways can be used [32, 33]. To sum up, in case of therapeutic failure, surgery is recommended.

Thoracentesis

Repeated thoracentesis are used for both to establish the diagnosis and to drain lymph from the pleural cavity [25]. Further, Selle et al. considered that in the newborn and the idiopathic chylothorax, thoracentesis may have favorable therapeutic outcomes [25]. Other authors advice to abandon repetitive thoracentesis in newborn and young children in favor of minimal pleurectomy when chylothorax is restoring [20, 24]. Favorable results were obtained in the case of posttraumatic chylous fistula [24].

In most cases, repeated thoracentesis is not a method of treatment with favorable outcomes, the applicability of this method being generally with diagnosis purpose. The next step is to establish pleural drainage by performing minimal pleurectomy.

Surgical Treatment

Thoracic Drainage Procedure

It is an intermediary therapeutic initiative between conservative and major surgery;

sometimes it may be the only therapeutic gesture associated with complete parenteral therapy. It can be applied both for diagnostic purposes, by biochemical and cellular analysis of the drained liquid through the chest tube as well as for the therapeutic purpose. Pleural drainage can resolve respiratory functional disorders in rapid and large accumulations, by expanding lung parenchyma and allowing for close monitoring of lymphatic lesions, according to which therapeutic response is established.

In children and infants, losing small amounts of lymph may have a devastating effect for disease progression. In these patients monitoring of lymphorrhea should be extremely rigorous because any change in hydroelectrolytic and nutritional homeostasis is perceived more acutely than in adults.

When there is low lymph drainage, a diet containing medium chain triglycerides can be established. In most cases, however, this diet is insufficient to close the fistula. The unfavorable progression, with the increase in lymphorrhage, will require a parenteral nutritional treatment complete with discontinuation of oral intake.

A passive drainage system is indicated do not increase lymphatic leakage by increasing negative intrathoracic pressure, latter being a factor that is favoring the maintenance and even enlargement of the fistula. If the evolution is favorable with decreasing or stopping lymphatic leakage, pleural drainage is suppressed. If lymphorrhage persists, minimal pleurectomy will be associated with other therapeutic maneuvers to suppress lymphatic fistula.

From our experience, we consider that pleural drainage by minimal pleurectomy can only stop lymphorrhage when associated with conservative treatment methods, with a role in decreasing lymph flow, in situations where there are lesions in lymphatic collaterals with low lymphatic pressure.

Loss of the lymph through the thoracic duct injury requires complex surgery, either by minimal invasive techniques or by thoracotomy: ligation of the thoracic duct to which it is associated:

– Partial parietal pleurectomy;
– Mechanical and chemical pleurodesis (talc, doxycycline, betadine);
– Pleuropulmonary decortication in case of "localization" of the lymphatic collection.

Minimal Pleurectomy Associated with Chemical Pleurodesis

Pleurectomy associated pleurodesis is an alternative treatment method. The principle consists in making the pleuro-pulmonary adhesions, which produce a close symphysis to allow for the closure of the fistula. This method consists of placing 10 grams of talc in 20 ml of glucose, saline or 1% lidocaine on the drainage tube under expanded lung conditions. Talc may be replaced with doxycycline solution for injection. In order to ensure a uniform distribution of pleurodesis substance in the pleural space, it is necessary to mobilize the patient in different positions.

However, there are discussions about the difficulty of major surgery after pleurodesis, imposed by the persistence of lymphatic leakage, which makes this therapeutic method less practical. Also, in most cases, the chylothorax has benign etiology, which makes the use of talc more and more rare. There are authors who mention the possibility of pulmonary thromboembolism (TEP) and adult respiratory distress syndrome (ARDS) by intrapleural application of talc [34, 35]. So that, we consider as effective alternative to pleural talc, pleurodesis with betadine (iodopovidone) which is also an extremely effective sclerosing agent. It can be administered either on the drain tube or intraoperatively in variable concentration, extrapolating from the demonstrated effectiveness of betadine in neoplastic pleural effusion. We are using 100 ml of 5% betadine solution.

Useful therapeutic algorithm proposed by Joseph Miller (2000) aims (Fig. 3) [36]:

- Diagnosis confirmation followed by pleural drainage by introducing a chest tube to monitor lymphatic leakage;
- Under conditions of total parenteral nutrition, lymph drainage is monitored for 7–14 days:

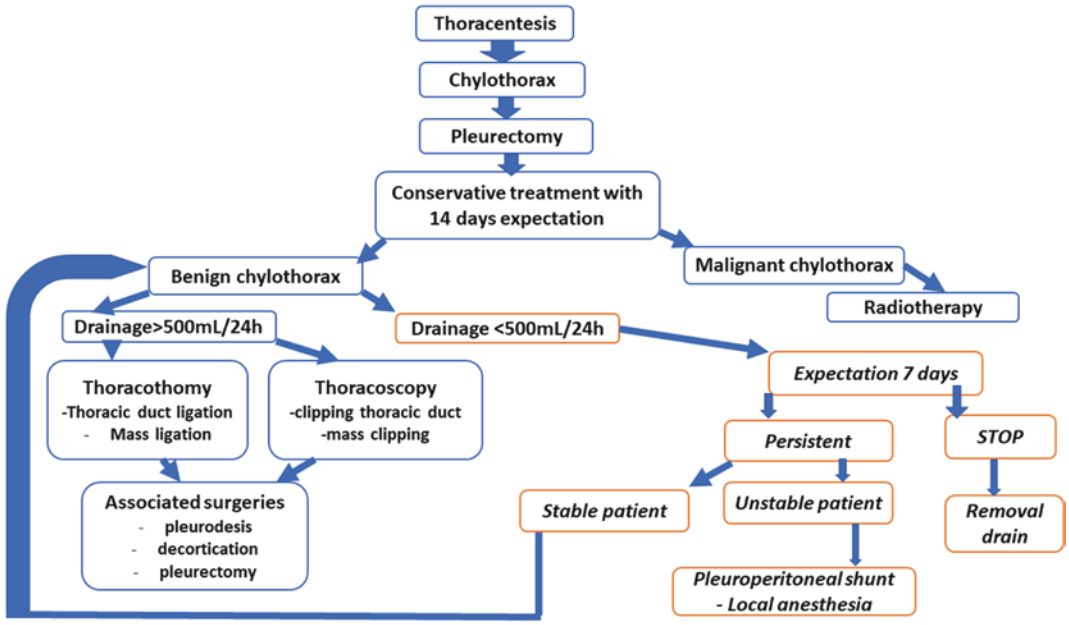

Fig. 3 Proposal of therapeutic algorithm in chylotorax (modified from Miller) [36]

- drainage >500 ml/24 h → toracotomy with thoracic duct ligation, pleurectomy—decortication
- drainage <250 ml/24 h → extending of conservative treatment with continuous monitoring of chylous drainage for one week.

The cessation of lymph drainage by drainage tube requires the test with fatty food:

- the absence of lymphorrhage requires the drainage suppression;
- the recurrence of lymph drainage requires various surgical maneuvers:
  - Pleuroperitoneal shunt (in malnutrition);
  - Thoracotomy with thoracic duct ligation, associated with pleurectomy—decortication (in hemodynamically, nutritional and immunological balanced patient);

With the introduction of minimally invasive methods, video-assisted thoracoscopic surgery (VATS) gradually replaces classical surgery.

It is to be noted that the above mentioned therapeutic algorithm applies to secondary thoracic duct lesions due to non-malignant cause. In the forms associated with a malignant tumor, radiotherapy with 2000 rads is performed, with very good results (Fig. 3) [36].

Minimally Invasive Surgical Procedures

Thoracoscopic Surgery

It is an effective method in the treatment of postoperative chylotorax, due to low morbidity, high success rates and low costs [37–42]. It is recommended for the early treatment of postoperative chylotorax. By this technique, it can be achieved chemical or mechanical pleurodesis, clips on thoracic duct, double ligation, or applying fibrin-glue [43–46].

Surgery is performed on the non-ventilated lung through selective intubation with prior administration of 50–100 ml of cream 1–2 hours before surgery. The surgery can be performed using two or three ports (Fig. 4) [1, 42, 44, 47].

We performed the minimal invasive approach through two ports: 7/8 intercostal right space on the anterior axillary line and 5/6 intercostal right space on the mean axillary line. The oblique

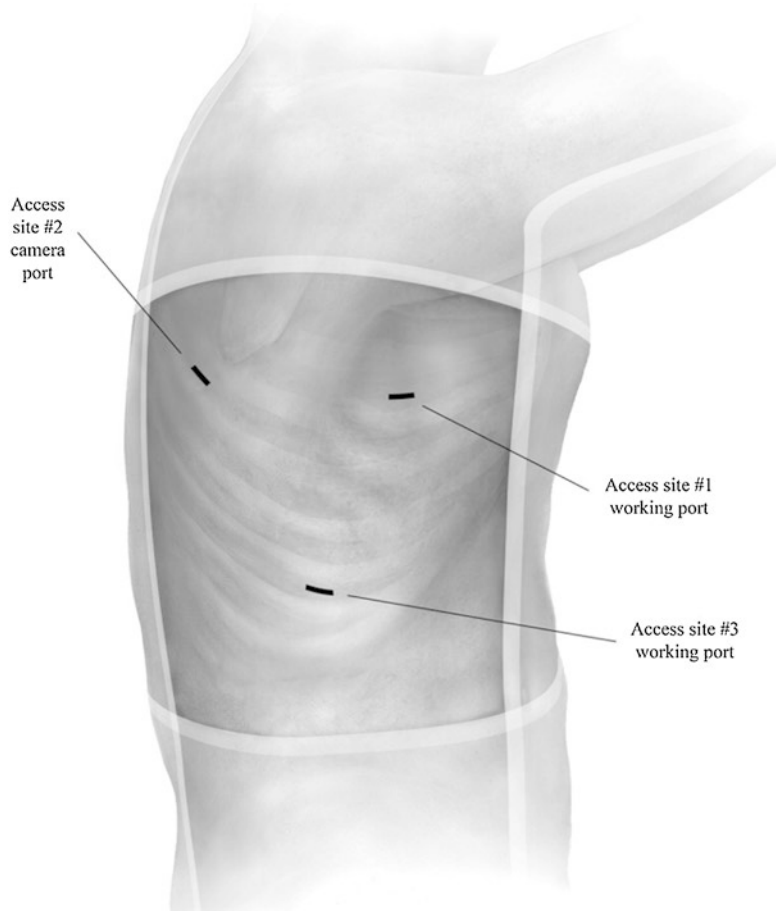

Fig. 4 Patient positioning and placement of incisions. From [1] with **permission**

view telescope can be inserted alternately through the two ports, along with the other thoracoscopic instruments: sternal saw, retractor, monopolar Hook electrical dissection loop, surgical stapler, forceps, scissors, and even biopsy brush.

After removal of lung with lung retractor, mediastinal pleura is incised from the esophageal hiatus to the right lower pulmonary vein. The thoracic duct and the place of the leak are highlighted (Fig. 5). We consider that precise identification of the thoracic duct (Fig. 6) without confusion with other anatomical elements around it is done by partial partitioning or sectioning it with great attention and only after its isolation from the other structures of the neighborhood; this maneuver confirms the presence of the thoracic duct by viewing "iatrogenic lymphorrhage" (Fig. 7). Complete sectioning can lead to retraction of the thoracic duct ends, making it difficult to identify them later in order to apply clips. At the time of the dissection of the thoracic duct, we must pay attention to the possible presence of some important collateral branches with supra-diaphragmatic localization or even the presence of thoracic duct abnormalities that must be identified with ligation. Their unidentified presence can be the cause of the surgery's failure, i.e. the persistence of the chylotorax. Lymph leakage is stopped either by ligation of both ends with non-resorbable threads or surgical stappling (Fig. 8).

If the thoracic duct is not identified, we consider that the **mass ligation** (Fig. 9) [1] of the

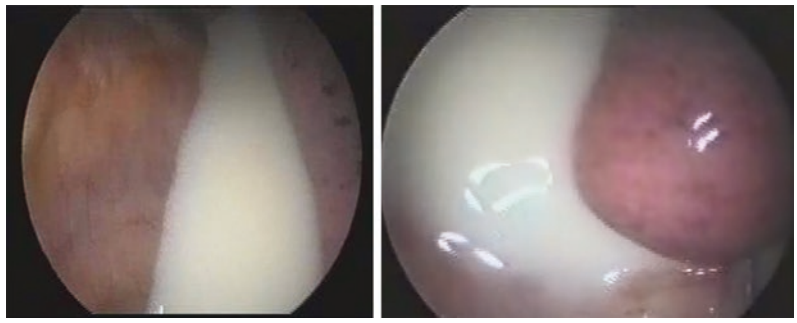

Fig. 5 Intraoperative aspect (thoracoscopic surgery): presence of milky liquid in the right pleural cavity

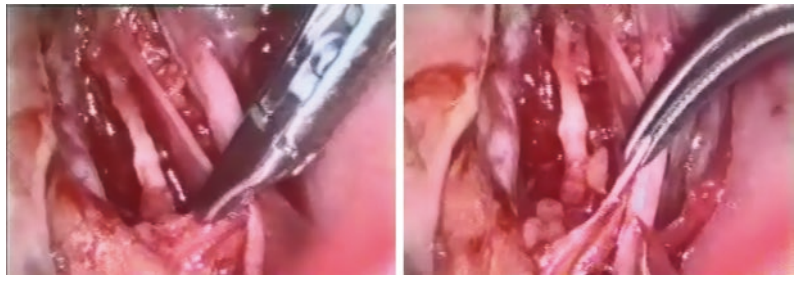

Fig. 6 Thoracoscopic appearance: thoracic duct filled of lymph at the level of azygoesophageal area

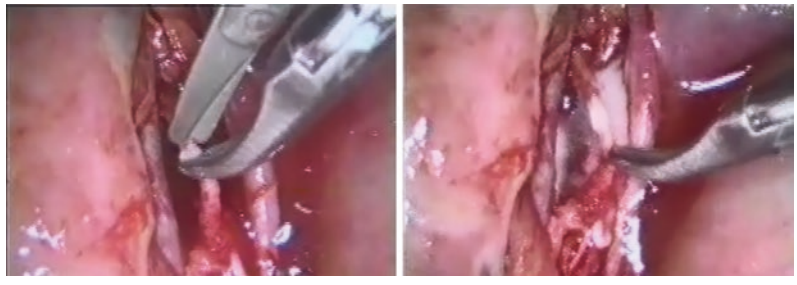

Fig. 7 Thoracoscopic appearance: **a** confirming the presence of the thoracic duct—its sectioning with the instrument of mini-invasive surgery; and **b** extravasation of lymph in the wound after its sectioning

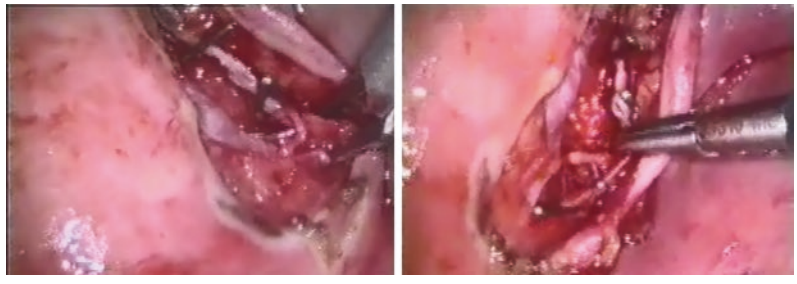

Fig. 8 Thoracoscopic appearance: Double stappling of thoracic duct (above and below the ductal wound) as well as stappling/clipping of a collateral intercostal lymphatic vessel

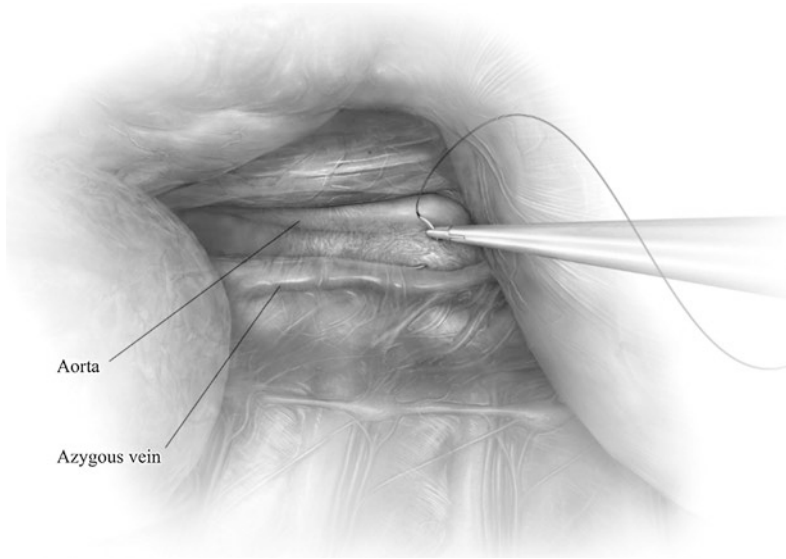

Fig. 9 Mass ligation. From [1] with **permission**

tissues located between the aorta, spine, esophagus, pericardium, vena azygos, according to the technique popularized by Patterson and described by Murphy and Piper, can successfully solve these cases [48, 49].

If the chylous fistula is located in the upper part of the thoracic duct, try ligation of the duct at the Poirier's triangle located between the internal carotid artery, the aortic arch and the spine [50].

Video-Assisted Thoracoscopic Surgery (VATS)

It is another minimally invasive method that maintains the same principles as the technique mentioned above, with the disadvantage of performing a minithoracotomy of about 5 cm which can affect respiratory functional status, especially in patients with associated pathologies or malnutrition.

It is usually applicable in conditions of poor technical infrastructure or limited professional experience in the thoracoscopic solution regarding the pathology of the thoracic duct [51].

We believe that the ligation of thoracic duct along with neighboring tissue—the Patterson procedure—can be performed with increased safety through this approach in situations where there are variants of origin or thoracic duct with connections between the branches of origin.

Wurnig et al. mentions the ligature of the thoracic duct and the pericardial window in the case of a chylothorax associated with chylopericardium, by video-assisted surgery, considered by the authors to be an effective method of surgical treatment with low morbidity [51].

Thoracoscopic minimally invasive techniques can be applied to traumatic thoracic canal lesions in the cervical region, sometimes difficult to be solve at the level of wound bed and associated with chylotorax.

The use of intravenous fibrin-glue may be a way of solving the fistula [22, 46].

We used TachoSil patches no matter of the level of lymphorrhage as an alternative, safe but not indispensable option in solving the chylous fistula.

Major Surgical Procedures

Of particular importance is the moment of surgical intervention, which remains controversial [49, 52, 53].

Preoperative preparation to view fistula by administration of cream or olive oil (100–200 ml) is mandatory (see cervical chylous

fistula). If the thoracic duct lesion can not be easily identified to be clipped in order to minimize trauma of the thoracic duct wall, it is good to abandon extensive dissection to identify the site of the lesion and to proceed further with the supradiaphragmatic ligation.

The Lampson Procedure

This surgical procedure was introduced in 1948 by Lampson [54] and represents the classical technique of direct ligation of the thoracic duct by thoracotomy.

A posterolateral approach is needed to achieve an easy approach to the thoracic duct. It is important to know the anatomical course, so that you can decide the way you approach it.

In unilateral chylothorax, a ipsilateral thoracotomy will be chosen.

In the right chylotorax, the approach of thoracic duct is done supradiaphragmatic at the level of vertebrae X-VIII [23], where it appears to be the most constant location, being located on the spine between the aorta and the azygos vein. A right posterolateral thoracotomy is required, the VII-VIII intercostal spaces, with sectioning the mediastinal pleura and the triangular ligament up to the inferior pulmonary vein.

In left chylothorax, the thoracic duct can be approached at the thoracic vertebrae level IV-V through left posterolateral lateral thoracotomy. At this level, the thoracic duct changes its tract by passing on the back of the esophagus to the right of the left. Another approach is quoted in literature at the Poirrier's triangle, near the left subclavian artery. The thoracotomy should be performed on the ipsilateral side to allow concomitant ligation of the thoracic duct and draining of lymph by pleurectomy ± decortication.

When chylothorax is bilateral, it is necessary to intervene by right posterolateral thoracotomy, with the supradiaphragmatic double ligation, due to the accessibility of the thoracic duct on this side. Later, if necessary, approaching on the left side when ligation of the thoracic duct by right thoracotomy was not effective. In these situations, an anomalous lymphatic duct can be suspected. Careful examination of the region is required to see if there are chylous leaks. This process also involves performing of a pleurodesis of the pleural cavity.

Once the chylous fistula is discovered, a laborious dissection of the thoracic duct is contraindicated, as there is a risk of another lesion, especially in a child where the tissues are more fragile [24].

Double ligation is preferred, instead of the use of metal clips that have the disadvantage of the thoracic duct injury at the application site [24]. Published evidence supports the ligation of the thoracic duct on the Teflon pieces in order to avoid injury to the wound [20].

Treatment of chylotorax by ligation of the thoracic duct has reduced the mortality rate from 50% to 15% [20].

Patterson Procedure

It is recommended if the fistulae orrifice can not be seen or when there are multiple lymphatic channels.

This technique consists in the "mass ligation" of all tissues on the right side of thoracic aorta and in front of the vertebral bodies, respectively the region between the aorta, esophagus and the azygos system immediately above the diaphragm [23].

Posterolateral thoracotomy is performed through intercostal space VII or VIII either on the right or the left side, the right side being preferred. Sutures of "mass" uses non-resorbable threads, with wires being recommended. It is not advisable to cut between ligatures of the tissue "block".

Some authors consider that the ligation of the thoracic duct can cause the appearance of the chylous ascites by retrograde ligation stasis and the increase of hydrostatic pressure at the level of the cisterna chyli [55].

Most authors recommend ligation of the thoracic duct at any level because it has been shown not to have severe consequences on the general condition. In the early days, the lymph pressure from upstream of the ligature may increase to 50 cm. By developing a collateral circulation, in a relatively short time (2–3 weeks), the pressure of the thoracic duct is decreasing slowly.

This surgical technique is a saving therapeutic method that can replace the Lampson procedure in cases of unidentifiable fistulae or in the case of initial surgical therapy failure.

Partial Parietal Pleurectomy

Ligation of the thoracic duct may sometimes be associated with partial pleurectomy, which in turn may be a singular therapeutic method in the chylotorax. Parietal pleurectomy aims to achieve a strong symphysis to abolish the chylous fistula. When there is a symphysis in the pleural cavity with the occurrence of a regional pleural thichening, either due to a previous pleuro-pulmonary pathology or due to a previous surgery, pleuropulmonary decortication may be associated with the thoracic duct ligation [20].

We believe that when there is visceral pleural thickening following previous pleural-pulmonary lesions and the lung fails to expand intraoperatively, this method may be associated with classical surgical techniques to increase the efficacy of the surgery. It can be used as a unique solution for solving lymphorrhage in the case of lesions of the branches of the thoracic duct and a total expansion of the pulmonary parenchyma; compression of the lymph leakage between the lung parenchyma and the thoracic wall may result in "closing" the fistula.

Transabdominal Ligation

It is a difficult technique due to the retroaortic approach, which is why it does not have broad applicability. The thoracic duct originates in the abdomen through a dilatation called the cisterna chyli, which is located at vertebral L2 level, right and retroaortically in the vicinity of the right pillar of the diaphragm, penetrating the thorax through the aortic hiatus. The course and length of the thoracic duct in the abdominal cavity makes it difficult to approach it. However, transabdominal ligation can be especially applied to patients whose general condition does not allow for chest approach where the functional impact is much greater [23].

Laparoscopic approach of the thoracic duct with transhiatal ligation is quoted in the literature after a right pleurectomy with chylotorax, performed for diffuse malignant mesothelioma [56].

Other Techniques

There are various other techniques to try to solve the fistula but the majority have been abandoned due to unsatisfactory results:

- anastomosis of the thoracic duct at the azygos vein [23] or external jugular vein;
- anastomosis of the ends of thoracic duct with non-resorbable monofilament threads (historical interest);
- venous patch on the fistula (historical interest);
- pleuro-venous shunt (the drainage of chyle into the right atrium by the saphenous and femoral veins—Kirkland)—abandoned technique due to poor results [24, 57].
- embolization of the thoracic duct—in thoracic duct lesions [58].

Pleuroperitoneal Shunt

The pleuroperitoneal shunt with Denver device is an alternative surgical method applicable to chylotorax [20, 59]. It aims the recovery of lymph from the peritoneal cavity, where the absorption capacity of the peritoneum plays a major role. This technique has been used by many surgeons, including Azizkau et al. in newborns with a secondary chylothorax due to upper vein thrombosis [60, 61].

According to Miller's therapeutic algorithm this method is indicated in relapses, when lymphorrhage reappears due to retaking of the normal diet [62]. It is also an indication for chylotorax in patients with associated severe pathologies or severe malnutrition, those who do not qualify for major surgery, as well as neoplasms. Using this unidirectional drainage device has the advantage of reducing protein losses by lowering the impact on the nutritional and immunological status of the patient.

We have not found any cases of chylous ascites secondary to pleuroperitoneal drainage.

Although this method is a small surgical technique, which can be applied to with associated severe pathologies or severe malnutrition, it also presents the disadvantage of the necessity of repeated manual "pumping" of the shunt, taking into account the pressional differences of the two cavities: positive—the abdominal compartment and negative—thoracic compartment [24, 63–65].

Mechanical Ventilation

Another method of treatment associated or singularly applied, in extreme situations, can be positive pressure ventilation (PPV), which can reduce and even stop the lymph loss by means of a compression mechanism exerted by the lung on the thoracic duct, respectively on the fistula [23].

Radiotherapy

This therapeutic method is applied in cases of malignant, nontraumatic chylotorax, whose cause is proved to be tumor (carcinoma, mediastinal lymphoma). The radiation dose used is around 1500–2000 cGy administered in 10 sessions [24]. This dose is considered to have no major side effects. Physical asthenia, nausea, transient fatigue can occur as side effects. Irradiating treatment sometimes succeeds in inducing a pleural symphysis with satisfactory results leading to the closure of the fistula.

Self-study

1. Which statement is/are true:
   a. the thoracic duct injuries can occur at any anatomical level depending on the etiology.
   b. thoracentesis is used for both to establish the diagnosis and to drain lymph from the pleural cavity.
   c. pleureodesis can be made with talc powder or betadine (iodopovidone).
   d. pleuroperitoneal shunt with Denver device is an alternative surgical method applicable to chylotorax.

Answers

1. Which statement is true:
   a. CORRECT
   b. CORRECT
   c. CORRECT
   d. CORRECT

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Surgical Approaches and Investigation Techniques to the Mediastinal Lymph Nodes

Jon A. Lutz

Key Points

- Mediastinal staging of Non-Small Cell Lung Cancer is of paramount importance to determine the optimal treatment strategy.
- The negative predictive value of combined chest computed tomography/positron emission tomography for mediastinal lymph node metastasis is reasonably high for peripheral cT1a-c tumors.
- Invasive mediastinal staging is recommended for:
  - centrally located tumors
  - tumor size over 3 cm (cT2a and higher)
  - N1 positive lesions.
- Endobronchial ultrasound-needle aspiration (or combined with endoscopic ultrasound) has become the best first choice for invasive mediastinal staging.
- Surgical invasive staging has still a role to play in special circumstances:
  - specific mediastinal localization (e.g. aortopulmonary window)
  - when suspicion of mediastinal lymph node metastasis is still high after negative biopsy by endobronchial ultrasound
  - exclude persistency of N2 malignancy after neo-adjuvant therapy.

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Introduction

The lymphatic drainage of the lungs and the central function of the mediastinal lymph nodes have been first described 1929 by Rouvière [1]. More than twenty years later Cahan published the description of a pneumonectomy with radical mediastinal lymphadenectomy in a curative intend [2], followed years later by radical lobectomy [3]. This led to the wide acceptance of lymphadenectomy as an inherent part of any anatomic lung resection performed for the treatment of Non-small cell lung cancer (NSCLC).

The first reported surgical access to the mediastinum was the transsternal approach in the late 19th century [4]. It was a way to treat conditions of the anterior mediastinum, i.e. mainly benign tumors and infectious conditions. Specific access to the lymph nodes of the mediastinum in lung pathologies evolved from a supraclavicular incision [5, 6] to the still practiced mediastinoscopy [7]. A less invasive approach to the anterior mediastinum and the aortopulmonary window was yet lacking until Chamberlain described the anterior mediastinotomy [8].

However, the most dramatic evolution had yet to come. The avenue of the computed tomography (CT scan) in the 1970s [9], the maturation of positron emission tomography (PET) and the combination of both technique as PET/CT in the 1990s [10] completely changed the algorithms of diagnosis and staging for

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NSCLC. In parallel, transbronchial needle aspiration (TBNA) evolved to endobronchial ultrasound-guided (EBUS) needle aspiration (NA) in the early 21st century challenging the established surgical approaches to mediastinal lymph nodes [11]. Even if this chapter focusses on the approach to the mediastinum in case of NSCLC, the principles are also valid for other pathologies like lymphomas [12] or—with slight modifications—for esophageal cancer [13, 14].

Computed Tomography, Positron Emission Tomography and Image-Guided Biopsy

CT scan and its combination with PET as PET/CT have established as first steps in cancer staging [15]. If the sensitivity and specificity for mediastinal lymph node metastasis of contrast-enhanced CT scan range from 57 to 68% and 76 and 82%, respectively, PET—with fluorine-18 fluorodeoxyglucose as tracer—reaches values of 79–85% and 87–92%, respectively [16]. The combination of both imaging techniques, PET/CT, has a negative predictive value of 94% (95% CI 92–95%) for mediastinal lymph node metastasis of stage IA NSCLC [16], rendering invasive mediastinal staging unnecessary for this subgroup of patients (Fig. 1). For stage IB, the negative predictive value drops to 89% (95% CI 84–94%).

Image-guided percutaneous biopsy of the mediastinum is not the first choice when considering systematic mediastinal staging for NSCLC. Biopsy is mostly performed under CT guidance, but alternatives can be ultrasound, MRI or PET/CT navigation. There are different types of needles being used, depending on the suspected diagnosis. Core needle biopsy has shown some advantage in allowing multiple sampling and protecting against seeding along the needle trajectory. Image-guided procedures can be a good alternative to other more invasive procedures in patients with medical limitations. The risk of pneumothorax (10% up to 60% of procedures) must be kept in mind, but transthoracic approaches can be done in local anesthesia and allow access to virtually all mediastinal regions [17]. The access pathway to the anterior mediastinum can be parasternal, suprasternal, subxiphoidal or transsternal, whereas the posterior mediastinum can be reached through a paravertebral approach.

Endobronchial Ultrasound and Endoscopic Ultrasound

The 3rd edition of the American college of chest physicians (ACCP) guidelines for staging of NSCLC have put combined EBUS- and EUS-NA—if available—in the first row of further staging procedures for mediastinal staging

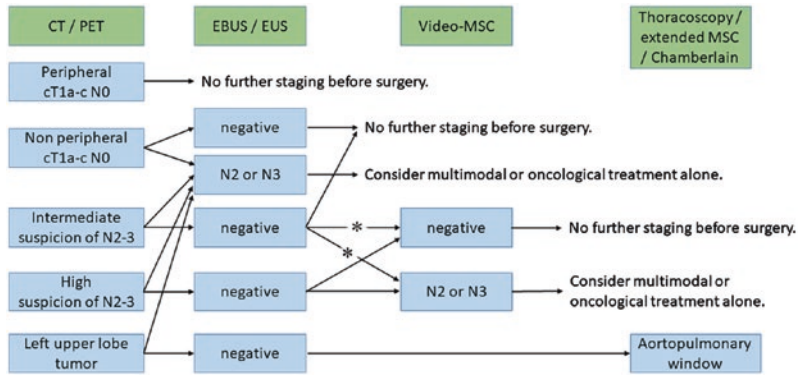

Fig. 1 Schematic algorithm for further mediastinal staging after PET/CT imaging, based on clinical practice guidelines from the ACCP [15]

after PET/CT imaging and is coherent with the revised European society of thoracic surgeons (ESTS) guidelines [15, 18]. If EBUS alone does not allow reaching lymph node station 5, 6, 8 and 9, combination with EUS gives a complete access to the mediastinal lymph nodes [19, 20]. In two prospective studies, the negative predictive value of the combined approach to exclude mediastinal lymph node metastasis was 96% (95% CI 90–99%), compared with mediastinoscopy ± anterior mediastinotomy as gold standard, and 91% (95% CI 83–96%), compared with transcervical extended bilateral mediastinal lymphadenectomy (TEMLA) [21, 22]. In a randomized controlled multicenter trial, combined EBUS and EUS (followed by surgical staging if negative) was compared to surgical mediastinal staging alone [23]. The negative predictive value was comparable between the combined EBUS and EUS vs surgical staging alone with 86% (95% CI 76–92%) versus 85% (95% CI 75–92%). Moreover, due to the stepwise approach, six patients with mediastinal lymph node metastasis could be identified by surgical mediastinal staging among the 65 patients without locally advanced disease after endosonography. Regarding complications, EBUS and EUS staging seems very safe with a 0.14% rate of severe adverse events (sepsis, mediastinitis, perforation, hemorrhagic complications or pneumothorax), 0.22% rate of adverse event (minor events requiring no intervention or hospital stay) and no mortality [24].

Videomediastinoscopy and Extended Videomediastinoscopy

Videomediastinoscopy replaced conventional mediastinoscopy in recent years [18]. Even if only trends towards higher lymph node yield and fewer complications (especially recurrent palsy) have been noted [25], the main advantage of videomediastinoscopy resides in the possibility of more standardization and facility of teaching. This technique has been even extended toward video-assisted mediastinoscopic lymphadenectomy [26], but at the cost of a higher rate of complications (5.9%). Maybe the most astonishing finding of this technique, also known as transcervical extended mediastinal lymphadenectomy, is a relatively high rate (5.7%) of N2 involvement of station 3 [27]. The flaws of the techniques are a mean operative time of 191 min and probably a higher rate of recurrent palsy of 4.8%, quite high values for a staging procedure. Call et al. demonstrate the technique in an illustrative fashion [28].

One condition where surgical staging has maintained its place is the restaging after induction therapy for locally advanced NSCLC [29]. Even if the study has been performed more than a decade ago and chemotherapy regimens evolved since, the main principle of neo-adjuvant treatment for locally advanced NSCLC is still patient selection between responders and non-responders. Hence, restaging between induction and planned anatomic resection has to be accurate. De Waele et al. showed that positive remediastinoscopy was linked to a significant poorer median survival of 14 months versus 28 months in case of negative remediastinoscopy and the relative risk of death was 1.99 (95% CI 1.2–3.3%).

Even if hemorrhage is a relatively seldom complication of mediastinoscopy (0.4%), its management remains challenging [30]. Most of the cases can be initially controlled by packing, but a majority requires salvage sternotomy. Postoperative mortality in case of hemorrhage is quite high (7%) and the median hospital stay climbs to 6 days.

Surgical Access to the Mediastinum: Anterior Mediastinotomy ("Chamberlain"), Videothoracoscopy (VATS), Sternotomy and Thoracotomy

Anterior mediastinotomy has only got a small place left in mediastinal staging for NSCLC (Fig. 1) [15, 18]. Endoscopic ultrasound-guided methods, extended mediastinoscopy and VATS surgery are alternatives. VATS allows to access all ipsilateral lymph node stations (Figs. 2 and 3) and permits to exclude pleural tumor infiltration. Sternotomy has only an anecdotic role, for example, when it is used as an access

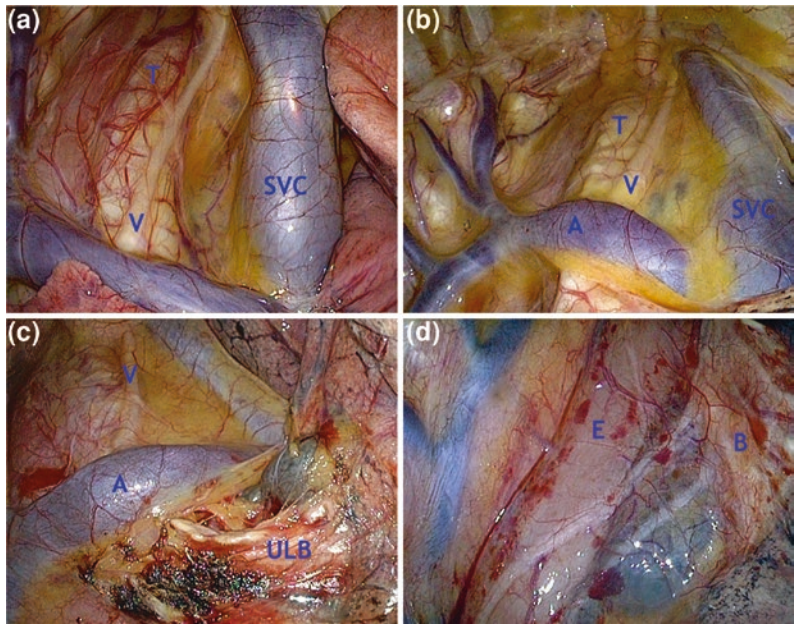

Fig. 2 Thoracoscopic view on right mediastinal lymph node stations. **a** Station 2R, **b** Station 4R, **c** Station 10R (hilar lymph node), D) Station 7

for performing another operation. Exploratory thoracotomy can begin with a mediastinal staging with frozen section and continue with pulmonary resection, but nowadays it is very seldom.

Mediastinal Lymph Nodes During Anatomic Resection

ESTS guidelines on intraoperative lymph node staging exist since 2006 [31]. They define different kinds of intraoperative lymph node assessment (selected lymph node biopsy, sampling, systematic nodal dissection, lobe-specific systematic node dissection and extended lymph node dissection). Standard recommendation is to perform a systematic nodal dissection, including en-bloc dissection of stations 2R, 4R, 7, 8 and 9 for right sided tumors, 4L, 5, 6, 7, 8 and 9 for left sided lesions. They propose to accept lobe-specific node dissection for T1 sized peripheral tumors.

Nevertheless, there is still a lot of controversies on mediastinal staging. The minimal number of resected lymph nodes has never been consensually defined like in other types of cancers [32]. Samayoa et al. recommend a lymphadenectomy of at least 10 nodes, but their database study showed a significant variation among centers in oncologic practice [33]. The concept of lobe-specific mediastinal node dissection for early stage, peripheral NSCLC has been explored in retrospective studies and seems to be a valid alternative to systematic lymphadenectomy, but needs more validation [34, 35].

The efficacy of lymphadenectomy practiced by VATS during anatomical resection has long been questioned. Two studies showed no disadvantage of the thoracoscopic approach in comparison to thoracotomy regarding number of mediastinal lymph node stations resected [36, 37]. Moreover, the view of the mediastinum during thoracoscopy is excellent and with the help of energy devices, the stations can be cleared in a radical way (Fig. 3c). The gain of popularity for sublobar anatomic resections makes more investigations on specific needs of fresh frozen analysis of intralobar lymph nodes and extent of mediastinal lymphadenectomy mandatory [38].

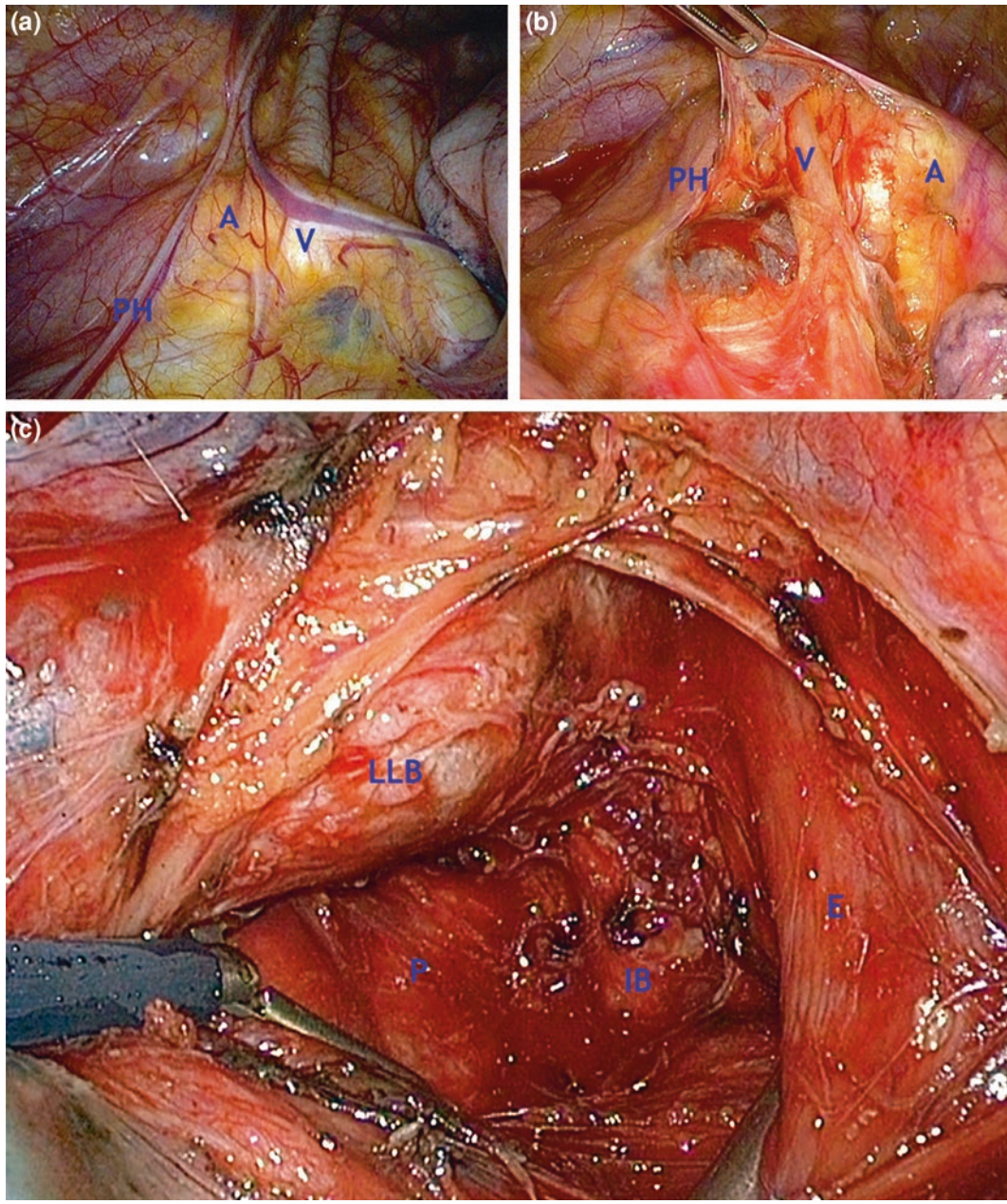

Fig. 3 Thoracoscopic view on left mediastinal lymph node stations. **a** Station 5, **b** Station 6 after opening of pleura, **c** Station 7 after radical lymphadenectomy

Finally, there are particular situations where guidelines recommendations are newly put in questions. Lim et al. plead for primary surgery in PET/CT positive N2 NSCLC if the tumor and the mediastinal lymph nodes are resectable [39]. An analysis of the combined database of the Society of Thoracic Surgeons (United States) and of the European Society of Thoracic Surgeons showed large differences in practice despite similar guidelines for N2 NSCLC [40]. This is seen as an opportunity to address these issues in a transatlantic study.

Conclusion/Summary

The developments of the techniques to investigate the mediastinum in the setting of NSCLC have led to the establishment of stepwise guidelines that seem to be valid [41, 42]. In the future, the most appropriate attitude regarding N2 resectable NSCLC and the strategy of hilar and mediastinal lymphadenectomy during segmentectomy will have to be specified.

Self-study

(1) Which mediastinal lymph node localization is accessible by EBUS-NA?
   a. Station 5
   b. Station 7
   c. Pulmonary ligament
   d. Station 4L.

(2) What is the next step after negative EBUS-NA mediastinal staging of an NSCLC with intermediate suspicion of N2-N3 (normal mediastinum in PET/CT but positive N1)?
   a. Repeat EBUS-NA
   b. Videomediastinoscopy
   c. Proceed to surgery
   d. Neo-adjuvant chemotherapy.

Answers

(1) Which mediastinal lymph node localization is accessible by EBUS-NA?
   a. Station 5
   b. Station 7—CORRECT!
   c. Pulmonary ligament
   d. Station 4L—CORRECT!

(2) What is the next step after negative EBUS-NA mediastinal staging of an NSCLC with intermediate suspicion of N2-N3 (e.g. normal mediastinum in PET/CT but positive N1)?
   a. Repeat EBUS-NA—Only if doubts about appropriate experience and skills of previous operator!
   b. Videomediastinoscopy—CORRECT!
   c. Proceed to surgery—Only if suspicion of mediastinal involvement does not remains high!
   d. Neo-adjuvant chemotherapy.

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The Thyroid Gland

Surgical Anatomy of the Thyroid Gland

John I. Lew, Josefina C. Farra, and Melissa L. Mao

Key Points

- The embryologic development of the thyroid gland accounts for the wide variation in anatomic variants.
- The thyroid gland is intimately associated with many neurovascular structures in the neck.
- Detailed knowledge of the course of the recurrent laryngeal nerves on each side of the neck is crucial to avoid injury and associated morbidity.

Embryology

The thyroid gland begins its development around the fourth gestational week. From the floor of the primitive pharynx, an endodermal thickening develops between the first and second pharyngeal pouches and forms the thyroid diverticulum. At this point, the diverticulum begins its descent in the anterior neck along a thin tract known as the thyroglossal duct, which connects the primitive thyroid to the base of the tongue. By week 7, the thyroid diverticulum has reached its final position in the lower neck, anterior to the trachea. In most cases, the thyroglossal duct is now obliterated, with its proximal remnant as a permanent pit on the tongue known as the foramen cecum. The distal remnant of the thyroglossal duct persists as a pyramidal lobe of the thyroid gland in approximately 50% of the population. During its descent, the thyroid diverticulum changes from a spherical shape to its final bilobar shape made of a median isthmus and two lateral lobes [1, 2].

Abnormal descent of the thyroid gland can occur, which results in ectopic thyroid tissue anywhere from the base of the tongue to the diaphragm. For example, failure of thyroglossal duct descent results in thyroid tissue at the base of the tongue, known as a lingual thyroid. Aberrant thyroid tissue in the mediastinum may occur due to malformations during the descent of the myocardium, as there exists a close relationship between the pharyngeal endoderm and the myocardial mesoderm [2]. This can result in a primary substernal goiter, in which fragments of thyroid tissue become separated and descend into the mediastinum. A primary substernal goiter has no attachment to the cervical thyroid, and as a result, receives its blood supply directly via mediastinal vessels [3].

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Functionality of the thyroid gland is noted around the third gestational month, at which time the first follicles containing colloid can be seen. The parafollicular C cells, which are responsible for producing calcitonin, are derived from neural crest cells from the fourth and fifth pharyngeal pouches [1].

Surgical Anatomy

The thyroid gland is a butterfly shaped organ located in the midline of the anterior lower neck at approximately the level of the second and third tracheal rings. The isthmus is directly attached to the anterior trachea, while the superior poles of the right and left thyroid lobes are directly attached to the anterolateral trachea and larynx. The typical thyroid gland weighs approximately 15–30 grams. When abnormal enlargement of the thyroid gland occurs, there may be extension into the mediastinum, known as a substernal goiter [1]. When there is continued downward growth of thyroid tissue originating from the thyrothymic ligament, this is known as a secondary substernal goiter. Conversely, a primary substernal goiter, which is far less common, is completely confined to the mediastinum and thought to originate from aberrant thyroid tissue [4].

The thyroid gland has a robust vascular supply via the superior and inferior thyroid arteries and their many anastomoses. The superior thyroid artery is the first branch of the external carotid artery, while the inferior thyroid artery is a branch of the thyrocervical trunk (off the subclavian artery). The venous drainage of the thyroid gland occurs through a plexus that ultimately drains into the internal jugular vein and brachiocephalic vein. In approximately 50% of patients, the middle thyroid vein is readily identifiable, coursing transversely from the mid to lower thyroid lobe, superficial to the common carotid artery, and draining into the internal jugular vein. In certain conditions, particularly Graves' disease, the thyroid gland is hypervascular and requires meticulous ligation of the blood supply [1].

A critical structure encountered during thyroidectomy is the recurrent laryngeal nerve (RLN), a branch of the vagus nerve. It is known as a recurrent nerve because after branching off the vagus, it courses back superiorly rather than continuing inferiorly with the path of the vagus nerve. A RLN exists on both the right and left side. The RLN innervates all of the intrinsic muscles of the larynx, except the cricothyroid, and is responsible for vocal cord function. Additionally, the RLN carries sensory information to the larynx, esophagus, and trachea. Damage to the RLN may result in voice hoarseness, aphonia, dysphagia, or aspiration. In the event of bilateral RLN injury, acute respiratory compromise may ensue with medialization of both vocal cords, which may require emergent tracheostomy [5].

Due to the morbidity associated with RLN injury, the surgeon must have detailed knowledge of its anatomic course, which differs slightly on each side. The right RLN loops under the right subclavian artery and then ascends the right paratracheal space at a slightly oblique angle before inserting into the larynx just posterior to the Ligament of Berry. The left RLN has a longer course which loops under the arch of the aorta at the ligamentum arteriosum before ascending in a vertical fashion along the tracheoesophageal groove. Although uncommon, a non-recurrent laryngeal nerve may exist, where it branches off the vagus nerve at the level of the cricoid cartilage and takes a transverse course towards the larynx. This more often occurs on the right side with the associated anomaly of a retroesophageal right subclavian artery that branches from the arch of the aorta [5].

The superior laryngeal nerve (SLN) is also a branch of the vagus nerve. The external branch of the superior laryngeal nerve (EBSLN) innervates the cricothyroid muscle, which controls voice pitch and projection. The EBSLN is located with varying relationships to the superior thyroid artery and the superior thyroid pole. Injury to the EBSLN occurs at a greater frequency than RLN injury, however, its morbidity is less profound and may be clinically undetectable [6].

Self-study

1. Which of the following statements is true regarding thyroid embryology?
   A. The thyroid gland reaches its final position in the anterior lower neck by gestational week 12.
   B. The distal end of the obliterated thyroglossal duct may persist as the isthmus of the thyroid.
   C. Parafollicular C cells are derived from neural crest cells and produce calcitonin.
   D. Ectopic thyroid tissue may occur anywhere from the base of the tongue to the sternal notch.
2. Which of the following statements is true regarding surgical anatomy of the thyroid?
   A. A non-recurrent laryngeal nerve will more often be encountered on the left.
   B. The superior and inferior thyroid arteries are branches off the common carotid artery.
   C. The right recurrent laryngeal nerve has a longer course and loops around the innominate artery.
   D. Unilateral injury to the recurrent laryngeal nerve may result in voice hoarseness, aphonia, dysphagia, or aspiration.

Answers

1. Which of the following statements is true regarding thyroid embryology?
   A. The thyroid gland reaches its final position in the anterior lower neck by gestational week 7.
   B. The distal end of the obliterated thyroglossal duct may persist as the pyramidal lobe of the thyroid.
   C. **Parafollicular C cells are derived from neural crest cells and produce calcitonin—CORRECT.**
   D. Ectopic thyroid tissue may occur anywhere from the base of the tongue to the diaphragm.
2. Which of the following statements is true regarding surgical anatomy of the thyroid?
   A. A non-recurrent laryngeal nerve will more often be encountered on the right.
   B. The superior thyroid artery is a branch off the external carotid artery and the inferior thyroid artery is a branch off the thryocervical trunk.
   C. The left recurrent laryngeal nerve has a longer course and loops around the arch of the aorta.
   D. **Unilateral injury to the recurrent laryngeal nerve may result in voice hoarseness, aphonia, dysphagia, or aspiration—CORRECT.**

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Surgical Approaches in Thyroid Pathology and Operative Techniques

John I. Lew, Josefina C. Farra, and Melissa L. Mao

Key Points

- A high index of suspicion is necessary to obtain appropriate preoperative imaging for substernal goiters.
- Even with substernal extension, thyroidectomy is often able to be achieved via a cervical approach.
- Several different thoracic approaches are available for thyroidectomy, including sternotomy, thoroacotomy, and video-assisted thoracoscopic surgery (VATS).

Surgical Indications

There is a wide array of both benign and malignant pathologies which warrant thyroidectomy. Biopsy proven malignancy and biopsy indeterminate thyroid nodules remain among the most common reasons for thyroidectomy. The most common thyroid malignancy is papillary thyroid carcinoma, followed by follicular thyroid carcinoma, medullary thyroid carcinoma, and rarely anaplastic thyroid carcinoma. Indeterminate nodules are designated by the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) as atypia or follicular lesion of undetermined significance (Bethesda category 3), suspicious for follicular or Hurthle cell neoplasm (Bethesda category 4), and suspicious for malignancy (Bethesda category 5). Recent advancements in genetic testing of indeterminate thyroid nodules can further increase the suspicion for malignancy to help guide surgical management [1, 2].

Benign thyroid conditions leading to thyroidectomy include symptomatic goiter, Graves' disease, and toxic goiter/nodule. In these circumstances, the enlarged thyroid may be limited to the neck, or may extend substernally. Physical exam findings indicative of a substernal component include Pemberton's sign, in which raising of the arms results in facial flushing due to venous compression by a substernal thyroid, or inability to palpate the entire thyroid gland. Thyroid ultrasound may fail to visualize the inferior most portion of the thyroid. The preferred diagnostic modality to fully image the thyroid gland in these cases is a computed tomography (CT) of the neck and chest. This will give valuable information regarding inferior extent into the mediastinum, posterior mediastinum involvement, relationship to vital vascular structures, and assessment of tracheal deviation/compression [1].

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Traditional Cervical Approach

Proper patient positioning is essential to achieve adequate exposure during thyroidectomy. Traditionally, the patient is supine with both arms tucked and a shoulder roll placed to slightly extend the neck. General anesthesia is induced and the patient is intubated, with the option of using a NIM endotracheal tube for intraoperative nerve monitoring. The method described here will reflect just one of many ways to approach the dissection of the thyroid gland. A Kocher incision is made approximately two fingerbreadths above the sternal notch. The platysma is opened and subplatysmal flaps are raised. The strap muscles are exposed, divided in the midline, and elevated off each thyroid lobe. The lateral attachments of the thyroid are freed to expose the space between the trachea and carotid sheath. Dissection begins with mobilization of the superior pole, followed by the inferior pole. An important tenet during thyroid surgery is to perform the dissection as close to the thyroid capsule as possible to avoid injury to the RLN and parathyroid glands. The RLN is often identified during mobilization of the inferior pole or near its insertion at the larynx during division of the Ligament of Berry. Care is taken to preserve the parathyroid glands. The same sequence is repeated for the other side if a total thyroidectomy is being performed.

Special Considerations for Combined Thoracic Approach

When faced with a massive substernal goiter, total thyroidectomy may not be achievable via a traditional cervical incision and an extracervical approach may be required (Figs. 1 and 2). High clinical suspicion of a substernal goiter is necessary to obtain appropriate preoperative imaging, in particular, a CT scan of the neck/chest. This allows for a well-prepared surgical plan, which should include a thoracic surgeon to be available for the combined thoracic approach if necessary. These approaches include sternotomy, thoracotomy, and VATS [3, 4].

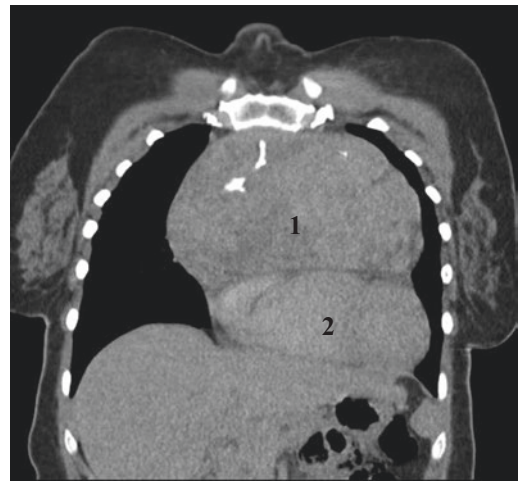

Fig. 1 CT scan of massive substernal goiter requiring cervical approach combined with sternotomy. *Note* 1 Thyroid gland; 2 Heart

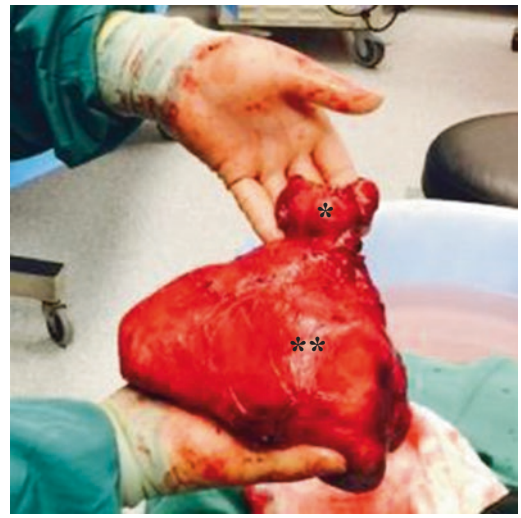

Fig. 2 Surgical specimen from Fig. 1 after successful removal. *Note* *Cervical thyroid gland; **Substernal thyroid

The question becomes when is it appropriate for a thoracic surgeon to become involved? Generally, the majority of substernal goiters can be delivered via standard cervical approach. However, this largely depends on the experience of the surgeon. Multiple grading systems have been proposed to classify substernal goiters based on their mediastinal extension to

help aid in surgical decision making. One of the more cited grading systems was developed by Cohen and Cho in 1994. They classified substernal goiters into four grades dependent upon the percentage of the goiter within the mediastinum: grade 1 with ≤25%, grade 2 with 26–50%, grade 3 with 51–75%, and grade 4 with >75% [5]. Despite this and the many classification schemes that have subsequently been proposed, there remains a lack of consensus on a universal grading system for substernal goiters.

Many studies have evaluated different risk factors that increase the likelihood of requiring a sternotomy for substernal goiter. Such risk factors include involvement of the posterior mediastinum, extension of the goiter to the level of the aortic arch or tracheal bifurcation, superior vena cava obstruction, malignancy with obliteration of clear surrounding tissue planes, emergent airway obstruction, longstanding history of substernal goiter, and increased thyroid tissue density [3, 4].

After mobilizing the thyroid gland as much as possible via cervical approach, an attempt is made to deliver the substernal component through the incision. If unable to safely mobilize the substernal component through the cervical incision, a thoracic surgeon may then perform a sternotomy. As the majority of substernal goiters are within the anterior mediastinum, this is commonly achieved through a median sternotomy. Depending on the size of the goiter and its inferior extension, partial sternotomy may suffice. A thoracotomy may provide improved visualization over sternotomy in the case of a posterior mediastinal goiter that extends below the aortic arch [6]. Since sternotomy or thoracotomy may add significant morbidity to the procedure, a combined cervical and VATS approach for substernal goiter has also been described with good outcomes while providing excellent exposure [7].

Complications

Thyroidectomy via cervical incision has an extremely low complication rate in the hands of an experienced surgeon. The major complications of thyroidectomy include bleeding, infection, injury to the recurrent laryngeal nerves, and injury to the parathyroid glands resulting in hypocalcemia. There appears to be higher rates of temporary vocal cord paresis and temporary hypocalcemia when a combined thoracic approach is required, although often not reaching statistical significance [8, 9].

However, there are significantly increased hospital lengths of stay and pulmonary complications with the addition of a thoracic approach. Increased hospital length of stay with the addition of a sternotomy is not unexpected, however, the duration of that stay is variable among the literature. The most notable pulmonary complications include pneumonia, atelectasis, pneumothorax, and pleural effusions. [8, 9] With experienced surgeons and a well-prepared preoperative surgical plan, additional complications incurred from a combined thoracic approach may be mitigated.

Self-study

1. Which of the following is true regarding a substernal goiter?
   A. If ultrasound fails to image the inferior most extent of the thyroid gland, a CT scan is the diagnostic imaging modality of choice.
   B. Thyroidectomy for a substernal goiter can rarely be achieved via cervical incision alone.
   C. Substernal goiters located in the anterior mediastinum may be better accessed via a thoracotomy.
   D. A physical exam finding which may indicate a substernal goiter includes Trousseau's sign.

2. Which of the following are acceptable thoracic approaches for thyroidectomy for substernal goiters?
   A. Sternotomy
   B. Thoracotomy
   C. VATS
   D. All of the above.

Answers

1. Which of the following is true regarding a substernal goiter?
   A. **If ultrasound fails to image the inferior most extent of the thyroid gland, a CT scan is the diagnostic imaging modality of choice.–CORRECT**
   B. Thyroidectomy for a substernal goiter can often be achieved via cervical incision alone.
   C. Substernal goiters located in the posterior mediastinum may be better accessed via a thoracotomy.
   D. A physical exam finding which may indicate a substernal goiter includes Pemberton's sign.

2. Which of the following are acceptable thoracic approaches for thyroidectomy for substernal goiters?
   A. Sternotomy
   B. Thoracotomy
   C. VATS
   D. **All of the above.–CORRECT**

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The Parathyroid Glands

Surgical Anatomy of the Parathyroid Glands

John I. Lew, Farra Josefina, and Mao L. Mellisa

Key Points

- The superior and inferior parathyroid glands have different embryologic origins.
- The inferior parathyroid glands are more commonly ectopic and may reside in a variety of locations.
- Knowledge of normal and ectopic parathyroid locations is key to successful parathyroidectomy.

Embryology

The parathyroid glands begin development around the fifth gestational week. There are typically four parathyroid glands that develop, a superior and inferior gland on each ipsilateral side. The superior parathyroid glands are derived from the endoderm of the fourth pharyngeal pouch, whereas the inferior parathyroid glands arise from the third pharyngeal pouch in close relationship with the thymus. Since the superior glands have a shorter course of migration to their final position, their location is more predictable, typically along the posterior aspect of the superior thyroid pole. As the thymus migrates caudally to its final position in the superior mediastinum, it pulls the inferior glands along with it, thereby creating a longer course of migration. The inferior glands will often separate from the thymus and reside in the area between the inferior thyroid pole and the superior portion of the thymus. Since the inferior parathyroid glands have a longer embryologic course and close development with the thymus, their location can be highly variable.

There are many embryologic abnormalities that account for the variations in parathyroid gland development. Supernumerary (greater than 4) glands have been reported in up to 13% of the population on autopsy studies. During migration of the parathyroid glands, cells may become separated from the main parathyroid mass and settle as rests of parathyroid tissue in ectopic locations. While these rests of tissue are much smaller than a normal parathyroid gland, conditions such as multiple endocrine neoplasia (MEN) syndrome and chronic kidney disease that result in parathyroid hyperplasia may cause growth of these rests into clinically apparent supernumerary parathyroid glands.

Ectopic parathyroid glands may occur as a result of failed or abnormal embryologic

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migration. Generally, it is the inferior parathyroid glands that reside in ectopic locations. The most common locations for ectopic glands include: intrathymic, tracheo-esophageal groove, carotid sheath, paratracheal and retro-esophageal areas, and intrathyroidal. Due to its migration with the thymus, if the inferior parathyroid gland does not separate during its course, it may reside within the mediastinum as far as the superior border of the pericardium.

The function of the parathyroid gland is derived from chief cells, which produce parathyroid hormone and regulate calcium homeostasis. These cells first appear at about 14 weeks gestation. The origin of the capsule that surrounds the parathyroid gland is not endodermal, rather, it is from neural crest cells. In the case of an intrathyroidal parathyroid gland, a distinct parathyroid capsule does not form.

Surgical Anatomy

The parathyroid glands are small oval-shaped organs measuring approximately 3–8 mm and weighing about 30–40 mg each, often likened to a lentil or grain of rice. The color is traditionally described as a yellowish to reddish brown. These qualities are not very specific, and it can be difficult to distinguish a parathyroid gland from adipose tissue, a lymph node, or an exophytic thyroid nodule.

The major blood supply to both the superior and inferior parathyroid glands comes from the inferior thyroid artery, a branch of the thyrocervical trunk which branches off the subclavian artery. However, the superior parathyroid glands also receive a portion of their blood supply via the superior thyroid artery. It is for this reason that during a four gland exploration, if three glands are identified as normal and the surgeon is unable to find the fourth inferior gland, an acceptable option would be to ligate the inferior thyroid artery on the side of the missing gland, in hopes to devascularize the hyperfunctioning parathyroid gland. Venous drainage occurs via thyroidal veins.

The superior parathyroid glands have a more consistent and predictable location. In general, the superior glands are located along the posterior aspect of the superior pole of the thyroid. To help identify the level of the superior gland, several anatomic landmarks must be identified. One landmark is the cricoid cartilage, where the superior gland can often be found at the level of its inferior border. Another landmark is the intersection of the recurrent laryngeal nerve (RLN) and inferior thyroid artery. The level of the superior gland is 1 cm above this intersection, within an area encompassed by a 2 cm diameter. The superior parathyroid is normally lateral to the recurrent laryngeal nerve.

The inferior parathyroid glands have a much less reliable location. Most commonly, an inferior gland is located between the inferior pole of the thyroid and the superior portion of the thymus, medial to the recurrent laryngeal nerve. The inferior parathyroid glands may be intimately associated with the RLN, and dissection of an inferior gland must proceed cautiously as to avoid nerve injury. Generally, the inferior glands have a more anterior position in relation to the thyroid, as opposed to the superior glands which are more posterior.

Unfortunately, there are cases where a four gland exploration fails to identify all four parathyroid glands. The most common location for a missing gland is at its normal anatomic position. However, the most common location for an ectopic gland is within the thymus, which may be accessible in the cervical region or deep within the mediastinum. Other ectopic locations include: tracheo-esophageal groove, carotid sheath, paratracheal and retro-esophageal areas, and intrathyroidal. Preoperative localization studies, including ultrasound, sestamibi scan, and 4D CT scans may aid in identifying the abnormal parathyroid gland. There are times where preoperative imaging studies fail to localize a parathyroid gland, and detailed knowledge of both normal and ectopic locations of parathyroid glands becomes even more essential during parathyroidectomy.

Self-study

1. Which of the following statements is true regarding parathyroid embryology?
   A. The superior parathyroid glands are derived from the fourth branchial cleft.
   B. The inferior parathyroid glands are derived from the third pharyngeal pouch.
   C. The superior parathyroid glands develop and migrate with the thymus.
   D. The inferior parathyroid glands have a more consistent location.

2. Which of the following statements is true regarding parathyroid anatomy?
   A. The sole blood supply to the parathyroid glands is via the inferior thyroid artery.
   B. The superior parathyroid gland can be found 1 cm inferior to the intersection of the recurrent laryngeal nerve and the inferior thyroid artery.
   C. The most common ectopic location of a parathyroid gland is in the thymus.
   D. If unable to find an inferior parathyroid gland, ligation of the superior thyroid artery may effectively devascularize the gland.

Answers

1. Which of the following statements is true regarding parathyroid embryology?
   A. The superior parathyroid glands are derived from the fourth pharyngeal pouch.
   B. **The inferior parathyroid glands are derived from the third pharyngeal pouch—CORRECT**.
   C. The inferior parathyroid glands develop and migrate with the thymus.
   D. The superior parathyroid glands have a more consistent location.

2. Which of the following statements is true regarding parathyroid anatomy?
   A. The blood supply to the parathyroid glands is via the inferior thyroid artery and superior thyroid artery.
   B. The superior parathyroid gland can be found 1 cm superior to the intersection of the recurrent laryngeal nerve and the inferior thyroid artery.
   C. **The most common ectopic location of a parathyroid gland is in the thymus—CORRECT**.
   D. If unable to find an inferior parathyroid gland, ligation of the inferior thyroid artery may effectively devascularize the gland.

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Surgical Approaches in Parathyroid Pathology and Operative Techniques

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Key Points

- Parathyroidectomy can often be accomplished via a cervical incision, using a focused approach.
- Although rare, mediastinal ectopic parathyroid adenomas may require a thoracic approach for complete excision and preoperative imaging studies for localization is critical.
- Thoracic approaches to parathyroidectomy include median sternotomy, partial sternotomy, anterior mediastinotomy, and VATS.

Indications for Surgery

Hyperparathyroidism remains the most common indication for parathyroidectomy. The vast majority of these cases are due to primary hyperparathyroidism (pHPT), in which a parathyroid gland(s) is autonomously hyperfunctioning, usually resulting in elevated PTH and calcium levels. Among cases of pHPT, most are due to a single adenoma, and less commonly, multiglandular hyperplasia. Other indications for parathyroidectomy include secondary and tertiary hyperparathyroidism, and the rare case of parathyroid carcinoma.

Fortunately, in the hands of experienced surgeons, initial parathyroidectomy has an extremely high success rate in achieving and maintaining eucalcemia. However, in the event of a failed parathyroidectomy or recurrence of hyperparathyroidism, redo parathyroidectomy can be problematic. It is paramount to have preoperative localization via ultrasound, sestamibi, and/or 4D CT scan to avoid blind exploration in a previously operated field and to identify ectopic parathyroid adenomas, which may be located in the neck or chest.

Traditional Cervical Approach

Like thyroidectomy, proper patient positioning is critical to achieve adequate exposure during parathyroidectomy. The positioning and setup for parathyroidectomy is essentially the same as that described for thyroidectomy, with the patient placed supine, both arms tucked, and a shoulder roll placed to slightly extend the neck. The procedure may be performed under local anesthesia or general anesthesia with the option

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of using a NIM endotracheal tube for intraoperative nerve monitoring.

The start of the procedure is similar to a thyroidectomy. A Kocher incision is made approximately two fingerbreadths above the sternal notch. The platysma is opened and subplatysmal flaps are raised. The strap muscles are exposed, divided in the midline, and elevated off each thyroid lobe. The lateral attachments of the thyroid are freed to expose the space between the trachea and carotid sheath. In searching for the superior parathyroid glands, the thyroid lobe will often have to be retracted medially in order to reveal the parathyroid gland located posteriorly to the thyroid lobe. As discussed above, the inferior parathyroid glands are located more anteriorly and often do not require much mobilization of the thyroid lobe. However, their location can be much more variable and require a more exhaustive search. A key principle during parathyroidectomy is to limit manipulation of the gland as much as possible. During a four gland exploration, once all glands are identified, the abnormal parathyroid gland is circumferentially dissected free from its surrounding attachments. Care is taken to avoid recurrent laryngeal nerve injury, particularly when isolating an inferior parathyroid gland.

If preoperative imaging studies have identified an abnormal parathyroid gland, a minimally invasive or focused approach may be employed. This involves directing the exploration and dissection only in the area identified by imaging (i.e. right inferior, right superior, left inferior, left superior). The size of the cervical incision, extent of dissection, and duration of surgery can be limited in this focused approach. Intraoperative PTH (ioPTH) monitoring is a well-described, widely-accepted adjunct to aid in successful focused parathyroidectomy. This method, pioneered and refined by Dr. George Irvin at the University of Miami in the 1990s, utilizes biochemical evidence to support removal of the pathologic parathyroid gland. ioPTH levels are drawn prior to cervical incision, prior to excision of the abnormal parathyroid gland, and then 5 minutes and 10 minutes post-excision of the gland. The Miami criterion requires a $\geq$50% ioPTH decrease at 10 minutes post-excision from the higher value of the pre-incision or pre-excision level. While there have been many modifications of the Miami criterion adopted at different institutions, the general premise remains the same [1].

Special Considerations for Thoracic Approach

Up to 2% of ectopic parathyroid glands located in the mediastinum may not be accessible via a standard cervical approach, typically those located below the brachiocephalic vein. Again, preoperative imaging using multimodalities should be obtained to delineate the anatomy and relationship of the ectopic gland to its surrounding structures (Figs. 1 and 2). While a sestamibi scan may indicate a mediastinal parathyroid

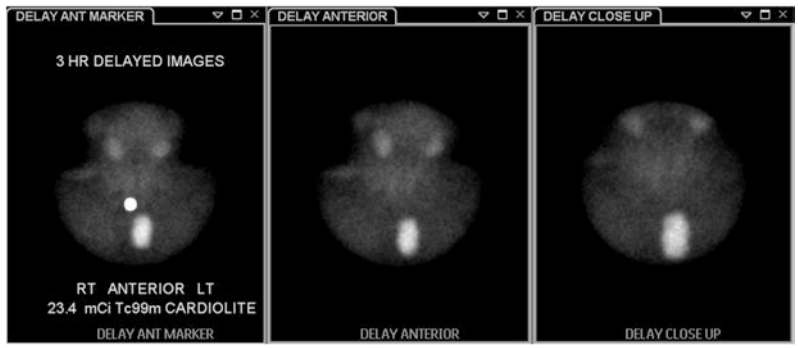

Fig. 1 Sestamibi scan of mediastinal parathyroid adenoma in a patient s/p failed 4-gland exploration via cervical approach

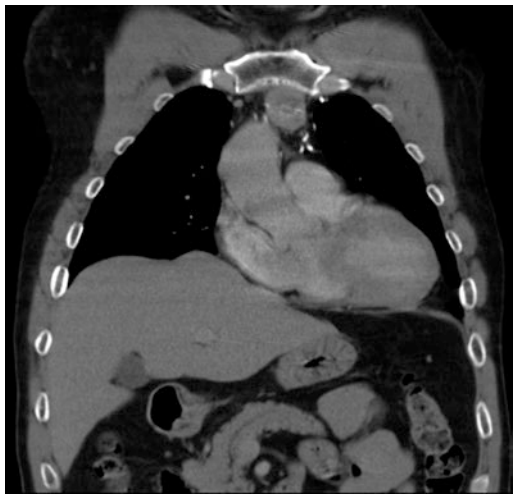

Fig. 2 CT scan of mediastinal parathyroid adenoma in a patient s/p failed 4-gland exploration via cervical approach, abutting great vessels key: *parathyroid adenoma

adenoma, it provides no structural details, and a follow up CT scan of the chest should be obtained. This allows for appropriate surgical planning and the inclusion of a thoracic surgeon during that planning [2].

Since the inferior parathyroid glands migrate embryologically with the thymus, when located ectopically in the mediastinum, they are found in the anterior compartment. It is worthwhile to attempt excision via a cervical approach by performing a cervical thymectomy. In most cases, the ectopic parathyroid gland can be successfully resected through this approach. However, during redo parathyroidectomy or if there are indistinct borders between the gland and mediastinal vessels, this blind approach may not be advisable. If a thoracic approach is necessary, this may be achieved via median sternotomy, partial sternotomy, video-assisted thoracoscopic surgery (VATS), or parasternal intercostal incision [2].

Traditionally, a full median sternotomy was performed when a mediastinal ectopic parathyroid adenoma could not be excised via cervical incision. As the trends in surgery are often geared towards becoming as minimally invasive as possible, recent literature has demonstrated that a partial upper sternotomy provides equally adequate exposure with less associated morbidity. Less invasive than a partial sternotomy, an anterior mediastinotomy approach has also been described with good exposure and operative outcomes. Briefly, this technique involves making a transverse incision overlying the costal cartilage and excising the costal cartilage to enter the mediastinum. This relies on precise preoperative imaging to identify the exact level of the parathyroid adenoma and choose the correct costal cartilage to excise. The least invasive approach is via VATS, which has also shown successful outcomes with low morbidity. VATS for resection of a mediastinal ectopic parathyroid adenoma has been performed with the patient in both supine and lateral positions [3–5]. Given this armamentarium of thoracic approaches, the choice is dependent upon the experience and comfort level of the thoracic surgeon.

Complications

For standard parathyroidectomy, complications include bleeding, infection, injury to recurrent laryngeal nerves, permanent hypoparathyroidism, or failed operation. These typically occur at such low rates that the vast majority of patients may be discharged home on the same day of surgery.

It is not surprising that if a median sternotomy is performed, the complication rates increase up to as high as 29%. Complications are typically pulmonary or wound-related, including wound dehiscence, mediastinitis, and pleural effusions. Additionally, there appears to be a higher incidence of recurrent laryngeal nerve injury, particularly in the setting of a reoperation. Minimizing this to a partial sternotomy has been shown to have significantly decreased complication rates, with the advantage of less post-operative pain and decreased length of stay [2].

In a recent series from the United Kingdom, VATS has shown promising results in a small series of patients. Although there was one conversion to thoracotomy for bleeding, all other

cases were successfully performed via VATS without any major complications and a median hospital stay of only 2 days [4].

Self-study

1. Which of the following statements is true regarding ectopic parathyroid adenomas?
   A. A mediastinal ectopic parathyroid adenoma will usually be found in the anterior mediastinum.
   B. Inferior parathyroid glands migrate embryologically with the thyroid gland and are often found intrathyroidal.
   C. If unable to identify an inferior parathyroid gland, it is reasonable to perform a sternotomy to evaluate for an intra-thymic parathyroid gland.
   D. Ectopic parathyroid adenomas may be found in the neck or abdomen.

2. Which of the following statements is true regarding thoracic approaches to mediastinal ectopic parathyroid adenomas?
   A. When a thoracic approach is required for parathyroidectomy, VATS appears to have the highest incidence of post-operative complications.
   B. Acceptable thoracic approaches include median sternotomy, partial sternotomy, anterior mediastinotomy, and VATS.
   C. A Sestamibi scan indicating a mediastinal parathyroid adenoma is sufficient preoperative imaging when planning a potential thoracic approach.
   D. When compared to full median sternotomy, a partial sternotomy has decreased risk of complications and longer hospital length of stay.

Answers

1. Which of the following statements is true regarding ectopic parathyroid adenomas?
   A. **A mediastinal ectopic parathyroid adenoma will usually be found in the anterior mediastinum—TRUE**.
   B. Inferior parathyroid glands migrate embryologically with the thymus and are often found intrathymic.
   C. If unable to identify an inferior parathyroid gland, it is reasonable to perform a cervical thymectomy to evaluate for an intra-thymic parathyroid gland.
   D. Ectopic parathyroid adenomas may be found in the neck or chest.

2. Which of the following statements is true regarding thoracic approaches to mediastinal ectopic parathyroid adenomas?
   A. When a thoracic approach is required for parathyroidectomy, full median sternotomy appears to have the highest incidence of post-operative complications.
   B. **Acceptable thoracic approaches include median sternotomy, partial sternotomy, anterior mediastinotomy, and VATS—TRUE**.
   C. A Sestamibi scan indicating a mediastinal parathyroid adenoma is insufficient preoperative imaging when planning a potential thoracic approach.
   D. When compared to full median sternotomy, a partial sternotomy has decreased risk of complications and shorter hospital length of stay.

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The Esophagus

Esophageal Anatomy

Mariano de Almeida Menezes, Guilherme de Godoy dos Santos, and Fernando Augusto Mardiros Herbella

Key Points

- Esophageal surgical anatomy is complex.
- Esophageal vascularization is poor but lymphatic drainage is exuberant.
- The esophagus is surrounded by important organ and structures that must be preserved during an operation.
- Surgical access to the esophagus may be accomplished by open or minimally invasive surgery. A cervical, thoracic, and/or abdominal route may be necessary.

Introduction

The esophagus is a hollow, tubular, flat organ divided in three different anatomic compartments: cervical, thoracic and abdominal. The thoracic esophagus should be further considered as 3 separate subsegments: upper, mid and lower thoracic [1, 2].

The esophageal wall is histologically comprised by the mucosa, submucosa, muscular layers and a tunica adventitia instead of a serosa found in other digestive organs. Subdivisions of these layers have oncologic significance. The mucosa comprises: epithelium (m1), lamina propria (m2), and muscularis mucosa (m3). The submucosa is formed by internal (sm1), medial (sm2) and external (sm3) layers. The muscular layer has 2 components: circular and longitudinal muscle fibers [3].

There are no dedicated blood vessels to supply the esophagus. It is vascularized by secondary branches of the thyroidal, bronquial and left gastric arteries. The venous drainage flows to the inferior thyroidal vein, azygos and hemi-azygos and left gastric vein [4].

Lymphatic drainage is exuberant in a longitudinal and intramural fashion due to abundance of lymphatic vessels in the submucosal layer, finally draining to the thoracic duct and the periesophageal lymphnodes. This anatomic peculiarity facilitates the spread of metastasis even in early stages of esophageal tumors [5].

Cervical Esophagus

The cervical part of the esophagus comprises a 5-cm segment, starting below the hypopharynx, roughly 15 cm from the incisors and continues to the thoracic inlet, approximately 20 cm from the incisors [6].

The cervical esophagus anatomically relates to the trachea and the thyroid gland anteriorly,

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to the cervical vertebrae posteriorly, and is sided by the carotid sheath bilaterally [7]. The esophagus is separated from the trachea by a thin connective tissue layer, in a close relation that renders tracheo-esophageal fistula very common in the esophageal cancer setting [8]. The tissue surrounding the cervical organs is loose and directly continues with the mediastinal loose tissue, enabling infection to spread rapidly from the neck to the mediastinum [8, 9].

This segment is supplied by the superior and inferior thyroidal arteries and minor branches from the common carotid and subclavian arteries. The inferior thyroidal vein drains this segment to the internal jugular vein [10].

Superior Esophageal Sphincter

Located in the cervical esophageal segment this sphincter is comprised by esophageal muscle fibers, cricopharyngeal and thyropharyngeal muscles, and the inferior pharyngeal constrictor muscle [11]. A weak area between the inferior laryngeal constrictor and the cricopharyngeal muscles enables the formation of the Zenker's diverticulum [12].

Recurrent Laryngeal Nerve

The right recurrent laryngeal nerve (RLN) originates from the right vagus nerve between the right subclavian artery and the sternal articulation. It loops beneath the subclavian artery and ascends upwards and to the right to the esophagus through the right tracheo-esophageal groove. The left recurrent laryngeal nerve is a branch of the left vagus that loops beneath the aortic arch before going through the left trachea-esophageal groove to left of the esophagus [13, 14].

Laryngeal nerves may be injured in up to 30% of the cases in a 3-field esophagectomy and these lesions may pose serious complications, which include aspiration pneumonia, the need for mechanical ventilation and tracheostomy [15]. Special care during the dissection of the superior thoracic segment of the esophagus as well as the cervical segment, combined with measures for sparing these nerves (i.e. continuous nerve stimulation) may warrant decreased incidence of this complication [15–19].

Surgical Approach to the Cervical Esophagus

The cervical esophagus is usually accessed during an esophagectomy to perform the digestive tract reconstruction and possible cervical lymphadenectomy, in cases of esophageal perforation or to treat Zenker's diverticulum [20].

Surgical access to the cervical esophagus is frequently performed through an oblique incision along the anterior border of the left sternocleidomastoid muscle with the head lightly tilted [21]. If a wider exposure is necessary (i.e. to a complete cervical lymphadenectomy) a bilateral collar incisional may be necessary (Fig. 1).

Along the carotid sheath and the interior jugular veins lie the lymph nodes that drain the cervical esophagus. The main lymphnode stations of interest are the VI and VII cervical lymphnode stations. The VI station comprises para-esophageal lymph nodes inferior to the hyoid bone and superior to the sternal pit, between the esophagus and the carotid artery. The VII station amounts to lymph nodes located below the sternal pit and above the artery inominata, posterior to the sternum and anterior to the esophagus [1, 22].

Thoracic Esophagus

The thoracic segment of the esophagus is 20 cm long, ranging from the superior thoracic inlet, 20 cm from incisor, to the esophageal hiatus in the diaphragm, 40 cm from incisor [6].

From a surgical point of view, the thoracic esophagus must be considered as three parts: upper, mid and lower.

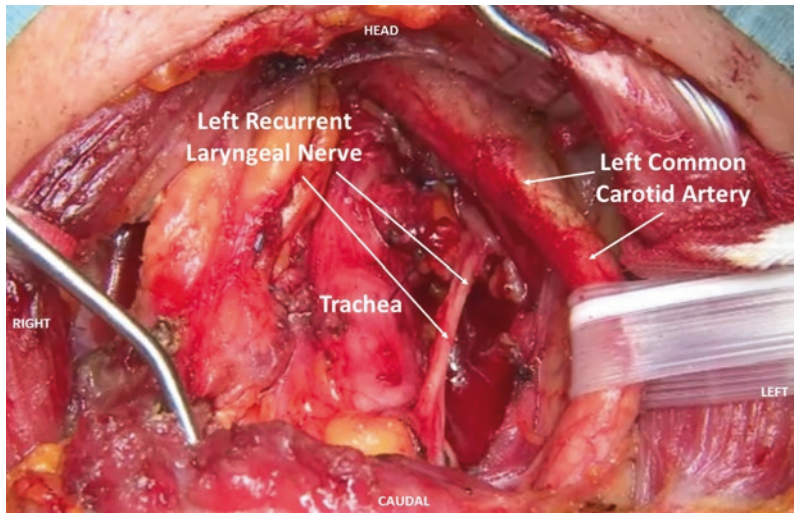

Fig. 1 Cervicotomy for esophageal exposure

Upper Thoracic Esophagus

The upper thoracic esophagus has around 5 cm, extending from the sternal notch to the azygos vein [23]. It corresponds to the endoscopist a distance between 20 and 25 cm from the incisors [6]. This segment is intimately adjacent to the trachea, which facilitates the occurrence of trachea-esophageal fistula in esophageal cancer [8]. This paratracheal fascia is included in the peri-esophageal lymphadenectomy during the "Pincers Maneuver"—performed in an "in block" resection of the surrounding membrane and lymphnodes of the trachea with the esophagus down to the laryngeal recurrent nerves inferiorly and up to the inferior thyroid artery superiorly [24].

At this level, the esophagus is limited upwards by the aortic arch, runs in between the ascending and the descending aorta through to the azygos vein. Other important neighboring vascular structures include to the right the brachium-cephalic artery and the superior vena cava and to the left the subclavian and common carotid arteries [23].

Both the recurrent laryngeal nerves arise in the upper mediastinum and runs closely to this segment of the esophagus [24].

The main lymphnode stations in this area are: (1) 1R—right lower cervical paratracheal nodes wich are amid the right supraclavicular paratracheal space and the right apex of the lung. (2) 2L—left lower cervical paratracheal nodes, located between the left supraclavicular paratracheal space and the apex of the lung. (3) 2R—right upper paratracheal nodes, stay amidst the intersection of the caudal margins of the brachio-cephalic artery with the trachea and the apex of the lung. (4) 2L—left upper paratracheal nodes located between the top of the aortic arch and the apex of the lung. (5) 4R—right lower paratracheal nodes, between the intersection of the caudal margins of the brachio-cephalic artery with the trachea and the cephalic border of the azygos vein. (6) 4L—left lower paratracheal nodes, are between the top of the aortic arch and the carina [1, 22].

Surgical Access

Surgical approach to the upper thoracic esophagus may be done from the neck. However, the thoracoscopic access enabled the dissection of this segment of the esophagus, as well as its lymphadenectomy in a safe manner with good results [25, 26].

Through a right thoracoscopy in prone position (Fig. 2) at the azygos vein's level the pleura is dissected on the dorsal side of the right vagus nerve toward the right subclavian artery that is surrounded by sympathetic perineurium. The next step is to expose the right RLN at the level of the right subclavian artery. The right tracehoesophageal artery and vein are ligated. In this moment is started the separation of the adventitia of the upper thoracic esophagus from the membranous wall of the trachea—Pincers Maneuver [24].

Middle Thoracic Esophagus

The middle thoracic esophagus has around 5 cm, extending from the level of the azygos vein to the level of the inferior pulmonary vein [23]. It corresponds to the endoscopist a distance between 25 and 30 cm from the incisors [6]. This segment has anatomical relations to the pulmonary hilum anteriorly, the thoracic vertebrae posteriorly, the pleura to the right and the descending aorta to the left [23].

The arterial supply to the esophagus derives from branches of the bronchial arteries and direct branches from the thoracic aorta across the levels from the 6th to the 9th thoracic vertebrae [10].

The lymphatic stations in this area are: (1) 7—subcarinal nodes are caudal to the carina of the trachea. (2) 8U—upper thoracic paraesophageal lymph nodes from the apex of the lung to the tracheal bifurcation. (3) 8M—middle thoracic paraesophageal lymph nodes from the tracheal bifurcation to the caudal margin of the inferior pulmonary vein [1, 22].

Azygos Vein

The azygos vein originates in the abdomen, entering the thoracic cavity through the aortic hiatus to the right of the aorta, ascending parallel to the thoracic vertebrae. At the level of the 4th thoracic vertebrae the vein crosses to the mediastinum and ends in the superior vena cava [13, 23]. Ligation of the azygos vein at its arch allows access to the middle thoracic esophagus, since the vein crosses over the organ at this point [27, 28].

Surgical Access to the Upper and Mid Thoracic Esophagus

Surgical approach is made at the 5th right intercostal space or a thoracoscopy may be performed. After access to the thoracic cavity,

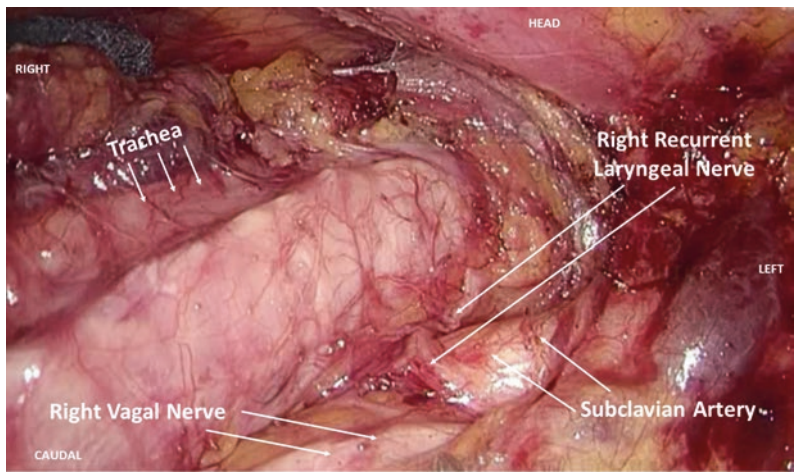

Fig. 2 Thoracotomy in prone position during dissection of the upper middle thorax

the lung is pushed to the side and the azygos vein is ligated, then the mediastinal pleura is opened to expose a free esophagus for facilitated dissection and local lymphadenectomy [29]. Some authors advocate a prone position to access the esophagus via thoracoscopy (Fig. 2). Anatomically, the prone position seems to grant better view of the posterior mediastinum. After ligation of the azygos vein and opening of the mediastinal pleura, the direct view of the middle and inferior esophagus, as well as its surrounding structures, allows for precise dissection, preservation of structures and thorough esophageal and lymphatic resection, without the inconvenience of the pulmonary structures, which are pushed down by gravity [30, 31]. This positioning places the posterior mediastinum in front, the posterior ribs and the thoracic duct are placed superiorly and the lungs inferiorly, the carina, the main bronchi, the aortic arch and the RLN are positioned inferior to the esophagus. The left RLN may be injured during dissection due to it's posterior position to the trachea [18, 19]. The caudal end holds the cardiac structures: right atrium and inferior pulmonary vein.

Lower Thoracic Esophagus

The lower thoracic esophagus has around 10 cm starting at the level of the inferior pulmonary vein to the level of the diaphragm's hiatus [23]. It corresponds to the endoscopist a distance between 30 to 40 cm from the incisors [6]. The esophagus bears anatomical relation to the pericardium (posterior wall of the left atrium) anteriorly, to the pre-vertebral fascia posteriorly, the aorta to the right and the parietal pleura to the left. At the level of the 8th thoracic vertebrae, the esophagus leans forward in order to enter the diaphragm hiatus, running in front of the descending thoracic aorta and between the inferior vena cava to the right and the parietal pleura to the left [23].

Thoracic Duct

The thoracic duct drains chyle from the cisterna chyli and enters the thorax trough the aortic hiatus. The structure rises through the posterior mediastinum between the thoracic aorta and the azygos vein, to the right of the esophagus [13]. At the level of the 4th to the 6th thoracic vertebrae, the duct crosses to the left side posteriorly to the esophagus and ascends to the superior mediastinum [13, 23]. It is recommended that during esophagectomies, the thoracic duct is dissected "en block" with the esophagus; [28] if this is not possible, though, mass ligation may be performed in order to avoid chylothorax, which may be present in 1% of the esophagectomies [29].

The main lymphatic stations surrounding the lower thoracic esophagus are: (1) 8Lo—lower thoracic paraesophageal lymph nodes from the caudal margin of the right inferior pulmonary vein and the esophagogastric junction (EGJ). (2) 9R—right pulmonary ligament nodes within the right pulmonary ligament and (3) 9L—left pulmonary ligament nodes within the left inferior pulmonary ligament. Lastly, (4) chain 15—diaphragmatic lymph nodes lying on the dome of the diaphragm and adjacent or behind its crura [1, 22].

Surgical Access to the Lower Thoracic Esophagus

Surgical approach to the lower thoracic esophagus is done through the esophageal hiatus after dissection of the abdominal esophagus and cutting of the diaphragm from the anterior border of the esophageal hiatus. This wide exposition allows thorough dissection and lymphadenectomy of the esophagus [27, 28].

The lower thoracic esophagus may be approached by left thoracotomy while the patient is positioned in right lateral decubitus, through incision of the 7th intercostal space or through

thoracoscopy. After accessing the thoracic cavity and moving aside the lung, for exposition of the pericardium and the mediastinal pleura, this tissue is opened through to the diaphragm, enabling dissection of the esophagus [32].

Abdominal Esophagus

The abdominal esophagus ranges from 2 to 6 cm, starting at the diaphragm crura and ending at the cardia by the angle of His. It may be absent in cases of hiatal hernia [6, 33].

Blood supply to the abdominal esophagus derives from branches of the inferior phrenic and the left gastric arteries. The left gastric vein is responsible for the venous drainage. The esophageal venous plexus communicates with the portal system, leading to esophageal varices in cases of portal hypertension [10].

The main lymph nodes stations at this location are: (1) 16—paracardial lymph nodes, immediately adjacent to the esophagogastric junction. (2) 17—left gastric lymph nodes, along the course of the left gastric artery. (3) 18—common hepatic lymph nodes, immediately on the proximal common common hepatic artery. (4) 19—splenic lymph nodes immediately on the proximal splenic artery. (5) 20—celiac lymph nodes at the base of the celiac trunk [1, 22].

Esophagogastric Junction

The esophagogastric junction is the transition between the esophagus and the stomach. It comprises the lower esophageal sphincter is a hypertonic area of the abdominal esophagus that relaxes during swallowing and which primary function is to avoid gastroesophageal reflux. This function may be impaired in the presence of hiatal hernia or if the abdominal esophagus is shorter than 2 cm [34].

Interestingly, the transition between the esophagus and the stomach is variable according to different methods (anatomic studies, endoscopy or manometry) since the mucosa transition does not necessarily coincide with the functional organ or to the transition between a sacular and a tubular organ. Anatomically, the transition is characterized by the peritoneal reflection on the stomach and by the adjacent region to the His angle [2]. The correct identification of the esophagogastric transition is important specially when approaching tumors of the cardia, since the positioning of the tumor's center sets the difference between esophageal tumors (Siewert I—up to 2 cm above the EGJ and II—between 2 cm above and 2 cm below the EGJ) and gastric tumors (Siwert III—below 2 cm from the EGJ) [1].

Diaphragm Crura

The right and left diaphragm crus form the esophageal hiatus and are composed by muscle tendons originating from the lumbar vertebrae. The abdominal aorta runs in front of these lumbar vertebrae and posterior to the esophageal hiatus. The inferior vena cava is located posteriorly and medially to the esophageal crura. As it crosses the esophageal hiatus, the esophagus is enveloped by the phrenoesophageal membrane, which originates from the reflection of the subdiaphragmatic fascia onto the transversalis fascia, as it lightly tilts the organ laterally and backwards to form the esophagogastric junction [33].

Vagus Nerve

The anatomy of the vagus nerve in the abdomen was of interest in the era of operations for peptic ulcer disease when a vagotomy was necessary most times. Latter, vagal-sparing esophagectomy renewed this interest but this procedure also did not lived long. The vagus nerve is characterized by nervous plexus surrounding the esophagus and it can present as four different anatomical variations as it courses along the thoracic esophagus. However, when it comes to the abdominal esophagus, the nerves ordinarily curve anteriorly to form the right vagus and posteriorly to form the left vagus [13, 33].

Surgical Access to the Abdominal Esophagus

The abdominal esophagus is best approached by laparotomy or laparoscopy (Fig. 3). An extensive thoracophrenolaparotomy was popular to treat distal esophageal cancer. The procedure starts with dissection of the esophageal membrane from the left diaphragm crus with excision of the fat patch. Afterwards the lesser gastric curve is accessed through the gastrohepatic ligament until exposition of the right diaphragm crus. Later dissection will range from the confluence of both the diaphragm crus to the zenith of the esophageal hiatus, freeing the diaphragm crura and the esophagus for safe structures dissection [26, 35].

Self-study

(1) Where recurrent laryngeal nerve cannot be injured during an esophagectomy:

(a) During esophageal dissection along the trachea in the neck
(b) During lymphadenectomy around the aortic arch
(c) During carinal lymphadenectomy
(d) During lymphadenectomy around the right subclavian artery.

Answer

(a) The right recurrent laryngeal nerve is located in the groove between the esophagus and the trachea
(b) The left nerve recurs at the aortic arch
(c) Both nerves (right and left) will have recurred at this level—CORRECT ANSWER
(d) The right nerve loops beneath the subclavian artery.

(2) These anatomical structures can be divided to access the esophagus without consequences:

(a) Azygous vein
(b) Thoracic duct
(c) Diaphragm
(d) Vagus nerve.

Answer

(a) Azygous vein arch is frequently divided to access the upper/mid thoracic esophagus
(b) The thoracic duct may be ligated without sequel. Duct ligation is a treatment for chylothorax
(c) The diaphragm may be sectioned and reconstructed to allow ample access to the

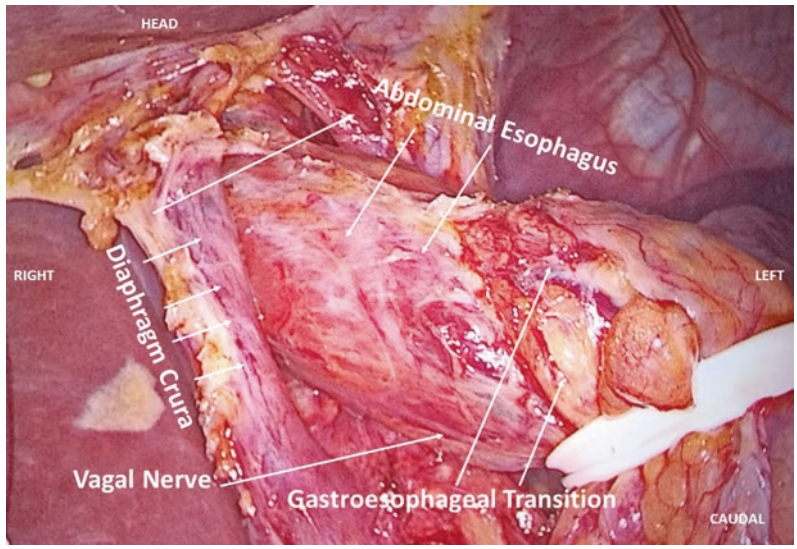

Fig. 3 Laparoscopy for dissection of the abdominal esophagus

distal esophagus when approached through the abdomen

(d) Vagus nerve injury may result in abdominal consequences such as delayed gastric emptying and diarrhea—CORRECT ANSWER.

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Surgical Approaches for the Esophagus

Byron D. Hughes, Kevin J. Hancock, Claire B. Cummins, and Ikenna C. Okereke

Key Points

1. Minimally invasive approaches can be performed for most patients requiring esophageal surgery.
2. When performing a minimally invasive Ivor Lewis esophagectomy, mobilizing the inferior pulmonary ligament fully will allow for greater retraction of the lung and better visualization of the esophagus.
3. When dividing the gastrohepatic ligament during esophageal surgery, ensure that there is not a replaced or accessory left hepatic artery.
4. When performing the neck dissection during esophageal surgery, do not place any retractors deeper than the sternocleidomastoid muscle to avoid injury to the recurrent laryngeal nerve.

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Cervical Esophageal Surgery—Techniques

1. Pharyngoesophageal diverticulectomy

Indication

Pulsion diverticula of the proximal esophagus (>2 cm)

Procedure Description

With the patient's head turned towards the right, an incision is made anterior to the sternocleidomastoid muscle 2 cm from the clavicle. The sternocleidomastoid is retracted laterally to expose the omohyoid muscle which is transected. The middle thyroid vein is identified, ligated and divided. The pharyngoesophageal diverticulum is typically visible at this point. A cricopharyngeal myotomy is performed by using a right angled instrument into the extramucosal plane and extended for about 5 cm. The diverticulum is then resected using a stapler. Care should be taken to dissect the diverticulum completely to identify its base and true connection to the esophagus. A common reason for recurrence is incomplete resection secondary to inadequate dissection and incomplete identification of the entire diverticulum.

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Pearls/Pitfalls

1. Endoscopic diverticulotomy is a minimally invasive option which may be conducted by using a flexible or rigid endoscope. It generally should be considered in patients who would not tolerate surgery well or who may have a technically challenging operation, such as patients who have had previous neck surgery or radiation to the neck area.
2. Esophageal manometry is a key element for work-up in patients suspected of having a Zenker's diverticula for dysphagia.

Thoracic Esophageal Surgery—Techniques

1. Ivor Lewis Esophagectomy

Indication

This technique is the most common approach we utilize for esophagectomy. Esophageal tumors located in the mid or distal esophagus are optimal for this approach. Our preference is to perform this operation using a minimally invasive approach, but the steps of the operation are very similar when performed open.

Procedure Description

The patient is placed in a supine position and general anesthesia using a double-lumen endotracheal tube is used to isolate the right lung during the thoracic portion of the case. The authors perform a flexible bronchoscopy to position the double-lumen tube and, in the case of mid-esophageal tumors, to evaluate for evidence of local invasion into the airway. Airway invasion would be a contraindication to surgery. To begin, a 5 millimeter (mm) or 10 mm port is placed in the left epigastrium. This serves as the camera port. The abdomen is then insufflated using carbon dioxide to a pressure of 15 millimeters of mercury (mmHg). A 10 mm port is placed in the right epigastrium. Two 5 mm ports are placed in the right upper quadrant, and one 5 mm port in the left upper quadrant (Fig. 1).

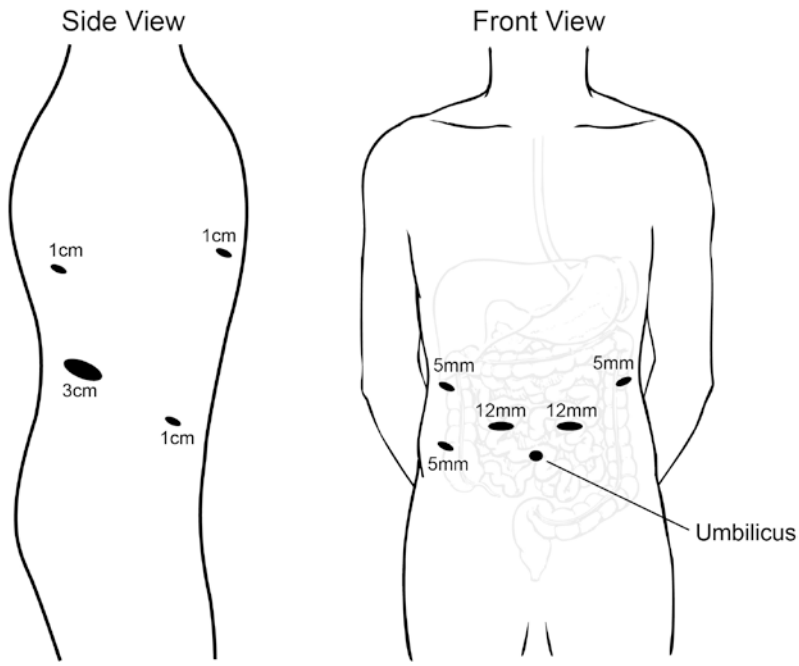

Fig. 1 Port size placement

The right-most port is used to place a retractor which elevates and retracts the left lateral segment of the liver. To begin the dissection, the gastrohepatic ligament along the lesser curvature is divided using an ultrasonic energy device. The dissection proceeds to the phrenoesophageal ligament, which is subsequently divided.

The greater curvature is then mobilized for approximately two thirds of its circumference. Releasing the avascular retroperitoneal attachments is important to allow the conduit to be mobile enough to reach the upper chest or neck if needed. A Kocher maneuver is also performed to increase mobility of the stomach.

With this mobilization the left gastric pedicle can be isolated with relative ease. The left gastric pedicle can then be divided using a vascular stapler. The division should be performed close to the retroperitoneum to remove as many lymph nodes as possible from this area.

Once the stomach has been completely mobilized, it can be divided to create the gastric conduit. Over time we have preferred to create a narrower conduit, approximately 3–5 centimeters (cm) in width. This width has reduced our rates of delayed gastric emptying. Making the conduit too narrow, however, may increase the risk of gastric tip necrosis.

A pyloromyotomy is then performed. Afterward, the gastric conduit is tied to the specimen to allow the conduit to be pulled up into the chest during the thoracic portion of the case. Finally, a jejunostomy tube is placed. We place the jejunostomy tube approximately 25–30 cm distal to the ligament of Treitz.

The patient is then placed in the left lateral decubitus position with slight rotation of the table toward the floor. The right chest is prepped and draped in usual sterile fashion. Next, four small incisions are made. A 3 cm oblique incision in the mid-axillary line is made in the 7th intercostal space and serves as the camera port and, ultimately, the entry site for the circular stapler. A 1 cm incision is made posteriorly in the 7th intercostal space, a 1 cm incision is made anteriorly in the 6th intercostal space just above the diaphragm and a 1 cm incision is made anteriorly in the 4th intercostal space. To begin the intrathoracic dissection, the inferior pulmonary ligament is divided and the right lung is retracted anteriorly. The esophagus is identified and the overlying pleura is divided. The thoracic esophagus is dissected circumferentially and a Penrose drain placed around it. The esophagus is then mobilized to the level of the azygous arch using the ultrasonic energy device. The azygous arch is divided using a vascular stapler to allow for room for the anastomosis. A mediastinal lymphadenectomy is performed in the paraesophageal area, pulmonary ligament and subcarinal areas.

After adequate mobilization, the esophagus is divided proximally using a linear stapler device close to the level of the azygous arch. The division can be performed more proximally for mid-esophageal lesions to obtain longitudinal margins of at least 5 cm. The distal esophagus and the stomach are then separated from the gastric conduit by cutting the sutures that were previously placed. The specimen is placed in an impermeable bag and removed through the utility incision.

To perform the anastomosis, a gastrostomy is created large enough to allow the stapling device to fit. Our preference is to perform an end-to-side anastomosis using a 25 mm circular stapler. The stapler goes through the gastrotomy. The anvil portion of the stapler is passed through the mouth to the esophageal stump, and then the metallic part of the anvil is poked through the esophagus. This metallic part should exit the esophageal stump not through the staple line on the stump.

Once the anastomosis has been created, an esophagogastroscopy is performed. The chest is filled with water to ensure that there is no air leak at the anastomosis. A nasogastric tube is inserted at this time. One chest tube or small bore drain is placed, using the camera port as the insertion site.

Pearls and Pitfalls

1. Prior to endoscopic stapling of the gastrohepatic ligament, the authors assess for a replaced left hepatic artery.
2. Ensure that there are two complete tissue donuts after creation of the esophagogastric anastomosis with the circular stapler.
3. Excessive tension placed on the greater curvature during mobilization of the stomach may lead to an inadvertent injury to the spleen.

2. **McKeown Esophagectomy (Tri-incisional Esophagectomy)**

Indication

Surgical approach for middle and upper esophageal carcinoma. This approach allows for more proximal esophagus to be resected than the Ivor Lewis approach. We also perform this surgery minimally invasively.

Procedure Description

The steps of this approach are similar to the Ivor Lewis approach, but with this approach the thoracic cavity is entered first. The ports are placed in the same position as the Ivor Lewis approach. The dissection of the esophagus should be performed up to the level of the thoracic inlet. Performing a very proximal dissection through the chest will facilitate mobilization of the esophagus in the neck.

Once the abdominal portion of the case has been completed, the cervical portion of the case is begun. If there are multiple teams present then the cervical and abdominal portions can be peformed simultaneously to decrease the overall operative time. A 3 cm oblique incision is made just anterior to the left sternocleidomastoid muscle. The platysma is divided. The omohyoid muscle is identified and divided. The esophagus is usually easily mobilized, and is elevated out of the neck. A linear stapler is used to transect the esophagus. An umbilical tie is secured to the esophagus prior to passing it into the abdomen.

The esophagus is then delivered into the abdomen, and the specimen is placed in an impermeable bag. The right epigastric port is opened to a width of 2 cm, which is usually enough to allow for removal of the specimen unless the tumor is very bulky. The umbilical tie is then secured to the chest tube, and passed toward the neck. The other end of the chest tube is secured to the gastric conduit. The gastric conduit is then delivered steadily into the neck. Care should be taken not to cause significant trauma to the conduit as it is passed cephalad.

To create the anastomosis, the esophagus and stomach are lined up side to side. A 60 mm linear stapler is passed into each lumen and the stapler is fired. The remaining anterior defect is closed using interrupted 2–0 silk stitches. Usually 6 to 8 stitches will be required to close the remaining defect.

The anastomosis should be drained. Our preference is to place a 10 Fr flat closed suction drain adjacent to the anastomosis.

Pearls and Pitfalls

1. Locate and avoid the recurrent laryngeal nerves during neck dissection to prevent injury.
2. Fewer pulmonary complications and less morbidity occur with a cervical esophagogastrostomy compared to an intra-thoracic anastomosis.
3. A chest radiograph in the operating room before extubation confirms full expansion of both lungs and proper placement of the nasogastric tube.
4. An anastomotic leak in the neck may occur in 3–10% of the time. If there is no evidence of an uncontrolled leak and the surgical drain is collecting all of the leak, then the neck incision does not have to be opened. The majority of cervical anastomotic leaks will heal with time.

3. Transhiatal Esophagectomy

Indication

Transhiatal esophagectomy works best for cancers of the lower third and gastroesophageal junction tumors. Though the transhiatal approach does not involve a thoracic incision, it does mobilize the entire thoracic esophagus and as such has been included in the thoracic portion of this chapter. Patients with poor pulmonary function tests may benefit from this procedure since it avoids a thoracic incision.

Our center does not perform this operation often, as this usually requires an open approach to mobilize the thoracic esophagus bluntly. We prefer a minimally invasive approach for almost all of our esophagectomies.

Procedure Description

The abdominal portion of this approach is the same as what has been described above, but a midline upper laparotomy is performed. Once the abdominal portion of the case has been completed, the esophagus is bluntly dissected in the mediastinum. This maneuver is performed by grasping the stomach at the gastroesophageal junction with one hand and sliding along the longitudinal fibers of the esophagus with the other hand. The dissection should be performed very delicately, especially at the levels of the carina and the azygous vein to avoid any potentially catastrophic injuries.

Once the blunt dissection has reached the level of the carina, the cervical incision is made. Finger dissection can be performed with one hand going down the neck and the other hand coming up from the abdomen until both hands meet. Eventually the esophagus can be freed completely.

The removal of the specimen and the anastomosis are performed in similar fashion to the previously described technique.

Pearls and Pitfalls

1. Limitations of the transhiatal approach include inability to perform an extensive mediastinal lymph node dissection.
2. Intraoperative monitoring of arterial blood pressure is necessary during mobilization of the thoracic esophagus to minimize hypotension due to cardiac displacement.
3. A narrow diameter gastric conduit is more prone to ischemia and a wide gastric conduit is prone to gastric stasis.
4. A chest radiograph in the operating room or immediately in the post-anesthesia care unit (PACU) should be performed to ensure full expansion of both lungs and proper placement of the nasogastric tube.

Abdominal Esophageal Surgery—Techniques

1. Laparoscopic Epiphrenic Diverticulectomy

Indication

Pulsion diverticula of the distal esophagus with esophageal motility disorder.

Procedure Description

Port placement is similar to the abdominal portion of an esophagectomy described above. The gastrohepatic ligament is divided with an ultrasonic energy device. The greater curvature is then mobilized for approximately 50% of the circumference of the stomach. These maneuvers allow for increased mobility of the stomach and distal esophagus, which will facilitate resection of the diverticulum.

Once the entire gastroesophageal junction has been mobilized, the diverticulum will be evident. The distal 5–7 cm of the esophagus are usually accessible from the abdomen, and the diverticulum can be completely dissected. Thereafter a linear stapler can be used to resect the diverticulum. The stapler should be placed directly parallel to the esophagus to prevent any aspect of the diverticulum from remaining. A 50 Fr bougie can be placed immediately before diverticulum stapling to prevent any narrowing of the esophagus.

On the contralateral side of the diverticulum, a myotomy is performed beginning at the level

of the diverticulum neck and carried distally for approximately 5 cm onto the cardia of the stomach. The author likes to perform a Dor fundoplication to cover the esophageal diverticulum and provide some degree of antireflux protection, but any fundoplication is appropriate.

Pearls and Pitfalls

1. Preoperative placement of an orogastric tube is rarely inserted due to the increased risk of diverticulum perforation.
2. Aspiration risk during intubation is reduced by prescribing a clear liquid diet for one week prior to the surgery.
3. A laparoscopic approach usually provides enhanced visualization compared to a thoracoscopic approach for epiphrenic diverticula.

2. **Laparoscopic Nissen Fundoplication**

Indication

Symptomatic reflux esophagitis refractory to medical therapy.

Procedure Description

The port position is similar to the previously described approaches. The dissection begins with the gastrohepatic ligament, followed by the greater curvature mobilization.

Once the hiatus has been mobilized, the right and left diaphragmatic crura are reapproximated using an 0 ethylene terephthalate suture. Usually 3 stitches are used to reapproximate the crura. Next, the fundus and greater curvature of the stomach is brought posterior to the esophagus and positioned for the 360° fundoplication. The stitch should go from the stomach to include a superficial level through the esophagus and then to the stomach on the other side of the esophagus. Going through the esophagus will help to prevent "slipping" of the wrap into the chest. When performing a complete 360° Nissen fundoplication, a 50 Fr bougie should be placed into the esophagus immediately prior to creating the fundoplication to prevent postoperative dysphagia from a tight wrap.

Pearls and Pitfalls

1. Our preference is to perform a water soluble contrast study immediately afterward but this test is not performed in many centers.
2. A 30° laparoscope will provide greater visibility.
3. To avoid minimizing the surgeon's mobility, the patient knees should only be slightly flexed.
4. Reverse Trendelenburg positioning during the case will improve visualization of the hiatus, especially in obese patients.

3. **Esophagomyotomy**

Indication

Achalasia
Diffuse esophageal spasm (DES).

Procedure Description

Port placement is similar to the other abdominal approaches described above. The dissection is similar as well.

The myotomy should be performed with an energy device, taking care not to injure the underlying mucosa. Our preference is to use a bipolar ultrasonic energy device, but a monopolar device can be used as well based on surgeon preference.

The myotomy is performed in the anterior aspect of the esophagus. The myotomy should proceed at least 5 cm above the gastresophageal junction and extend at least 5 cm onto the stomach. The most common reason for technical failure of the operation is from an incomplete distal myotomy onto the stomach.

After the myotomy is performed an anterior Dor fundoplication is performed. This fundoplication is created by wrapping the fundus and greater curvature of the stomach anteriorly. The fundus is then secured to the crural repair using interrupted stitches.

Pearls and Pitfalls

1. Preoperative manometry is essential for ensuring a correct diagnosis.
2. Preoperative EGD and/or upper gastrointestinal swallow should be considered in all patients, as benign tumors of the esophagus can create a clinical picture similar to achalasia but not necessarily be evident by manometry alone.
3. A Nissen fundoplication should be avoided due to high incidence of dysphagia when performed in patients with achalasia.
4. With regard to complete esophageal exposure, it may not be necessary to fully mobilize the posterior esophagus if the dilated portion is easily identifiable intraoperatively.

4. **Paraesophageal Hernia Repair**

Indication

Symptomatic paraesophageal hernias

Procedure Description

The port sites are positioned in similar fashion to the above approaches, but positioned more superiorly on the abdomen to allow the instruments to reach well into the mediastinum. This is especially important for very large paraesophageal hernias. Upon entry into the abdomen, the operation is begun by placing the patient in steep reverse Trendelenburg position.

The hernia should be reduced gently to avoid injuring any of the hernia contents. Once the hernia has been completely reduced, at least 5 cm of the esophagus should lie in the abdomen. If the esophagus is too short to allow this, a Collis gastroplasty should be performed. We perform the gastroplasty by creating a right-angle wedge resection of the cardia of the stomach. The gastroplasty is performed to lengthen the esophagus by 5 cm. A Nissen fundoplication is performed for patients with normal esophageal motility, while a partial fundoplication is used for patients with poor esophageal motility.

Pearls and Pitfalls

1. To assist in hiatal defect closure, the intraabdominal pressure should be decreased by reducing the insufflators pressure to 8–10 mmHg.
2. A Collis gastroplasty may be performed to increase the abdominal esophagus length.
3. A gastrostomy tube can be considered in elderly patients or very debilitated patients with poor tissue integrity. The gastrostomy tube acts to anchor the stomach onto the abdominal wall and prevent repeat herniation.

Self-study

1. Which of the following regarding cervical esophageal diverticula (Zenker's) is true?
   a. It is a true diverticulum with all layers of the esophagus involved.
   b. Division of the cricopharyngeus muscle is not necessary in some cases.
   c. Symptoms include regurgitation of undigested food and halitosis.
   d. Only minimal dissection around the circumference of the diverticulum is needed.
2. A patient with a carcinoma of the proximal esophagus, 5 centimeters below the sternal inlet, is an appropriate surgical candidate for surgical resection after staging workup. Of the approaches listed, which would be the best option for this patient?
   a. Transhiatal
   b. Thoracoabdominal
   c. Tri-incisional (McKeown)
   d. Ivor Lewis

Answers

1. Which of the following regarding cervical esophageal diverticula (Zenker's) is true?
   a. It is a true diverticulum with all layers of the esophagus involved—It is a false diverticulum.
   b. Division of the cricopharyngeus muscle is not necessary in some cases—This muscle has to be divided in every case, or the risk of esophageal fistula postoperatively and/or diverticular recurrence are high.

c. Symptoms include regurgitation of undigested food and halitosis**—Correct**.
d. Only minimal dissection around the circumference of the diverticulum is needed—A meticulous dissection around the diverticulum is required to establish the true boundaries of the diverticulum and not miss part of it when resecting it.

2. A patient with a carcinoma of the proximal esophagus, 3 centimeters below the sternal inlet, is an appropriate surgical candidate for surgical resection after staging workup. Of the approaches listed, which would be the best option for this patient?
   a. Transhiatal—Attempting blunt dissection of the tumor may be possible, but the risk of tumor disruption or injury to an intrathoracic structure, such as the trachea, is elevated with this approach. Though this approach may be possible with mid-esophageal lesions, this is not preferred.
   b. Thoracoabdominal—The exposure of the proximal esophagus is quite poor with this approach.
   c. Tri-incisional (McKeown)—**Correct**.
   d. Ivor Lewis—A lesion so proximal in the esophagus would be difficult to obtain adequate margins proximally while performing an Ivor Lewis esophagectomy.

Intraoperative Accidents and Complications in the Surgery of the Esophagus

Kazuo Koyanagi and Soji Ozawa

Key Points

- Intraoperative tracheobronchial and vascular injury during esophageal surgery are relatively rare, but serious and life-threatening complications once these accidents occur.
- Thorough preoperative workups, including review of relevant imaging, is important in detecting risk factors that associated with intraoperative complications, because prevention is the most reliable way to avoid them.
- When the tracheobronchial injury is recognized, endotracheal tube should be advanced beyond the injury point to control the airway, and then primary closure and/or appropriate patch or flap using vital organs should be performed based on the size and condition of the injury.
- When intraoperative major bleeding occurs, first, control the bleeding by pressure, next communicate with surgical team and operation staff about the situation and countermeasures, and then, if needed, request the support of cardiovascular surgeons.
- Intraoperative recurrent laryngeal nerve monitoring may be useful to identify the recurrent laryngeal nerve and prevent its postoperative paralysis.

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Introduction

The esophagus is a luminal organ from the neck to the abdomen and mainly exists in thoracic cavity. The esophagus is anatomically surrounded by important mediastinal organs, such as tracheobronchial airway, cardiovascular, nerve, and lymphatic systems. Therefore, intraoperative injuries of such organs may occur accidentally during the surgery of the esophagus. Although intraoperative injuries during esophagectomy are relatively rare, they cause serious and life-threatening conditions. Prevention is the most reliable way to avoid intraoperative accidents. Preoperative evaluation of surgical anatomies of the mediastinal organs and precise surgical procedures are recommended. Once such horrible accidents and complications occur, surgeons are required to be calm and to recover the injuries by appropriate procedures.

1. Intraoperative tracheobronchial injury

Injury to the major airways is rare, and its incidence is reported to be 0.8–1.8% during esophagectomy [1]. Although the tracheobronchial injury during esophagectomy may occur by double lumen endotracheal tube placement, most injuries are secondary to surgical procedures. Tracheobronchial injury is usually detected intraoperatively by recognition of massive air leak. The membranous portion

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of the trachea and bronchus is the most common location for the laceration, because of the close proximity to the esophagus. Transhiatal procedure may have more risk of membranous injuries when compared with transthoracic approach. Blind procedures around the esophagus may lead to damage to the tracheobronchial membrane. During transhiatal procedures, vertical tear of the tracheal membrane is the most experienced injury. Transthoracic approach is preferable to decrease the risk of tracheobronchial injury because surgeons can directly recognize the positional relationship between esophagus and trachea. The risks of intraoperative tracheobronchial injury increase when the esophageal tumors exist at the upper to the middle portion of the thoracic esophagus. Additionally, preoperative radiotherapy may create the fibrotic change between tracheobronchial membrane and esophagus and also induces the ischemic change. These abnormal conditions may increase the risk of tracheobronchial membranous injury. Thorough lymph node dissection around tracheobronchial tree may increase the risk of tracheobronchial lesions [2].

Tracheobronchial injury results in an inability to keep sufficient ventilation in the patient. Massive volume of air leaks through the tear, and the situation is life-threatening that has to be managed immediately. Aspiration of blood through the tears may cause the postoperative pneumonia and atelectasis. The inability of ventilation can be overcome by advancing the endotracheal tube beyond the laceration. When the endotracheal tube is advancing, careful handling, not to extend the tear, has to be recommended. After the control of the airway, the position of the patient should be converted to repair the tear acceptably under the direct visualization. To maintain the oxygenation in such situation, high-frequency jet ventilation or extracorporeal membrane oxygenation may be useful [3].

Primary closure and/or appropriate patch or flap using vital organs should be performed based on the size and condition of the injury. When the length of tear is short, e.g. less than 2 cm, only primary repair using absorbable suture is sufficient to close. When the length of tear is long or membranous tissue is considered not to be strong enough, primary closure followed by appropriate patch or flap using vital organs should be performed. Pericardium and mediastinal pleural patch may be useful to cover the site of primary closure. However, these patches are relatively poorly vascularized and sometimes not available because of previous therapy and tumor progression. The stomach tube with its omentum can be used to patch the tear. The stomach tube can fill dead-space of posterior mediastinum after esophagectomy and isolate the tracheobronchial membrane from other organs, increasing the local resistance to the infection. The use of synthetic materials is less attractive, because these materials need to be surgically removed later because of the infection induced by foreign materials. Subsequent stricture formation may occur when primary repair narrows the lumen or can only be performed under some tension. In such situation, pedunculated intercostal or dorsal muscle flap, that has a large volume and a rich blood flow, may be useful. Pedunculated muscle flap can cover the defect, fill the dead space, improve the wound healing, and control local infection. Although pedunculated muscle flap can be an important option for large tracheobronchial defect, adaptation of this method during esophagectomy is very few, because such large defect that cannot be repaired by primary closure is not caused by acute treatment during esophagectomy, but caused by chronic posterior mediastinitis [4].

Postoperatively, persistent or recurrent air leak through the chest drainage tube or subcutaneous emphysema at the face and cervical lesions means insufficiency of the surgical repair. Unless fully expanded lungs and well oxygenation, the patient immediately undergo reoperation to repair the lesion. If possible, positive pressure ventilation should not be used postoperatively. Even though the intraoperative tracheobronchial injury can be technically repaired, most patients suffer from postoperative

respiratory complications: use of artificial ventilation and longer ICU stay is required. Negative suction of chest tube should be used to expand the lung. Intensive respiratory physiotherapy and bronchial toileting are necessary, and antibiotics should be administered.

Intraoperative tracheobronchial injury has to be managed immediately because of its life-threatening situation. It is essential to keep the careful surgical procedures during esophagectomy. Once intraoperative tracheobronchial injury occurs, first, control the airway. Then, surgical procedures should be selected based on the extent and severity of the injury. Primary repair followed by appropriate patch or flap using vital organs may be sufficient to repair the injury.

2. Intraoperative vascular injury

Thoracic esophagus lies in close vicinity to major vessels such as aorta, pulmonary vein, and azygous vein, and it supplys mainly by small branches from the aorta. Due to the anatomical nature, major vascular injuries may occur during esophagectomy, resulting in life-threatening blood loss within a few seconds. When the tumor locates at middle of thoracic esophagus, risk of vascular injury increases [5]. Prevention is only the effective way to manage these serious complications. Preoperative 3D-CT imaging is useful for understanding the vascular anatomy (Fig. 1). However, unfortunately, once intraoperative major bleeding occurs, first, control the bleeding by pressure, then communicate with surgical team and operation staff about the situation and countermeasures. When vascular injuries occur during transhiatal and mediastinoscopic esophagectomy, thoracotomy on appropriate side should be performed. Also, minimally invasive procedure usually requires the conversion to open thoracic approach. Great vessel injury is often technically difficult to repair, and the support of cardiovascular surgeons should be considered in most cases.

Injury of proper esophageal artery and bronchial artery is the most experienced intraoperative bleeding during esophagectomy. If the root of the vessel remains, surgical clip and vessel sealing device can be used to arrest the hemostasis. If the blood vessel withdraws from its root of the descending aorta, pressure hemostasis should be tried. In many cases, bleeding can be stopped by only pressure hemostasis. Horizontal

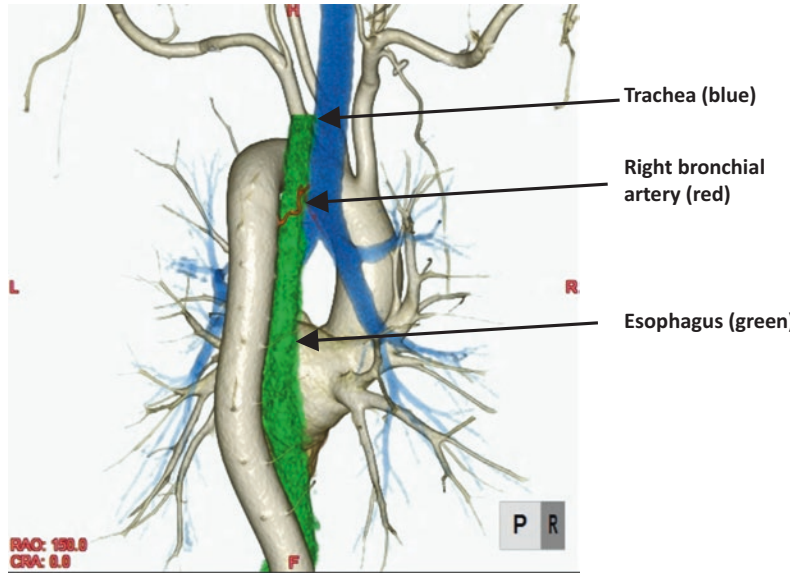

Fig. 1 3D-CT angiography (posterior view)

mattress suture with pledgets may be useful to close the bleeding point of the aorta.

Injury of descending aorta is extremely rare. In such a case, temporary hemostasis is sometimes very difficult. Try the compression by surgical gauze as much as possible. Then, peel the aortic wall circumferentially and tape the cranial and caudal side of the injury point of the aorta to manage massive bleeding. However, these procedures are unfamiliar to the gastrointestinal and thoracic surgeons, it is better to ask repair of the injury to cardiovascular surgeons. When performing an operation of aortoesophageal fistula, the thoracic endovascular aortic repair should be performed prior operation. Also, preoperative thoracic endovascular aortic may be useful if the tumor is suggested to be invaded to the aorta.

Injury of inferior pulmonary vein should be considered when the dissection of subcarinal lymph node is performed. Repair of right inferior pulmonary vein is easier than that of left inferior pulmonary vein. Open the pericardium, control the bleeding, and gently suture the vessel wall. Because the wall of pulmonary vein is very thin, care must be taken not to increase the damage. However, when the injury reaches the pulmonary parenchyma, aspiration of blood into alveoli occur, making sufficient ventilation impossible. In such a case, do not miss the timing to call the special surgeons.

Injury of superior pulmonary vein may occur during the dissection of left tracheobronchial lymph node. Repair of this injury often require the extracorporeal circulation system, so it is necessary to call cardiovascular surgeons immediately.

Prevention is the most effective way to avoid intraoperative vascular injury that is a life-threatening situation. Once intraoperative major bleeding occurs, control the bleeding immediately, next communicate with surgical team and operation staff about the situation and countermeasures, and then request the support of special surgeons if needed.

3. Injury of recurrent laryngeal nerve

The recurrent laryngeal nerves run in the tracheoesophageal grooves on both sides; the right recurrent nerve turns around the subclavian artery and runs cranially, and the left recurrent nerve turns around the aortic arch and runs up through the thoracic cavity before entering the cervical fields. Recurrent laryngeal nerve paralysis is a common and sometimes severe complication after esophagectomy. The dissection of thoracic paratracheal lymph nodes, especially along the recurrent laryngeal nerves, raises the risk of injury to the recurrent laryngeal nerves. The incidence of recurrent laryngeal nerve paralysis after esophagectomy has been reported to range from 0 to 50% [6]. The left recurrent laryngeal nerve has an increased risk of injury, compared with the right recurrent laryngeal nerve, because of its longer length.

Because the recurrent laryngeal nerve is a major motor nerve of the larynx and also gives off branches to the cricopharyngeal muscles which form the upper esophageal sphincter and play a pivotal role in swallowing, recurrent laryngeal nerve paralysis is closely related to impairments in breathing, speaking, coughing, and swallowing. Patients suffering from recurrent laryngeal nerve paralysis sometimes develop secondary respiratory complications, such as aspiration pneumonia and atelectasis; consequently, the duration of unexpected intubation and the patient's stay in the intensive care unit may be prolonged. In cases with bilateral recurrent laryngeal nerve paralysis, the bilateral vocal cords assume a median position, often leading to asphyxia and necessitating urgent reintubation or tracheotomy.

Injury to the recurrent laryngeal nerve is thought to result from damage caused by the electrocautery device, stretching, or compression of the nerve during esophagectomy. Therefore, efforts to prevent recurrent laryngeal nerve damage are essential for the postoperative management of patients undergoing an esophagectomy. Recently, the thoracoscopic procedure has been introduced as a minimally invasive esophagectomy, which might have a potential to reduce recurrent laryngeal nerve paralysis because of its magnified operative view obtained by thoracoscopy. However, the incidence of recurrent laryngeal nerve paralysis

did not reduce after introducing the minimally invasive esophagectomy [7]. In the minimally invasive esophagectomy, several kinds of electrocautery devices are frequently used. Despite the association of several factors, including stretching or compression of the nerve during surgery, with recurrent laryngeal nerve paralysis after esophagectomy, electrocautery devices is considered as a critical factor for recurrent laryngeal nerve paralysis. Surgeons should pay attention to the direct and indirect thermal injuries of recurrent laryngeal nerve especially during minimally invasive esophagectomy [8].

Intimate knowledge of normal and anatomic variants of the recurrent laryngeal nerve is very important for avoiding injury to the recurrent laryngeal nerve. Recently, new technique; intraoperative recurrent laryngeal nerve monitoring, has been introduced in esophageal cancer surgery. This technique has been widely used in thyroid and parathyroid surgery. It may be helpful to avoid the intraoperative injury of recurrent laryngeal nerve [9].

In cases with recurrent laryngeal nerve involvement via metastatic nodes, the recurrent laryngeal nerve is sometimes resected together with metastatic nodes to enable a curative operation. Laryngeal reinnervation should be considered in such cases, since this procedure can prevent the progressive loss of thyroarytenoid muscle tone and stiffness (Fig. 2) [10]. Recurrent laryngeal nerve reconstruction can improve phonation. The recurrent laryngeal nerve consists of adductor and abductor fibers that innervate adductor and abductor muscles, respectively. There is no spatial segregation of the nerve fibers. After the direct anastomosis of the served recurrent laryngeal nerve, the nerve fibers regenerate in a misdirected fashion. However, there are two to four times as

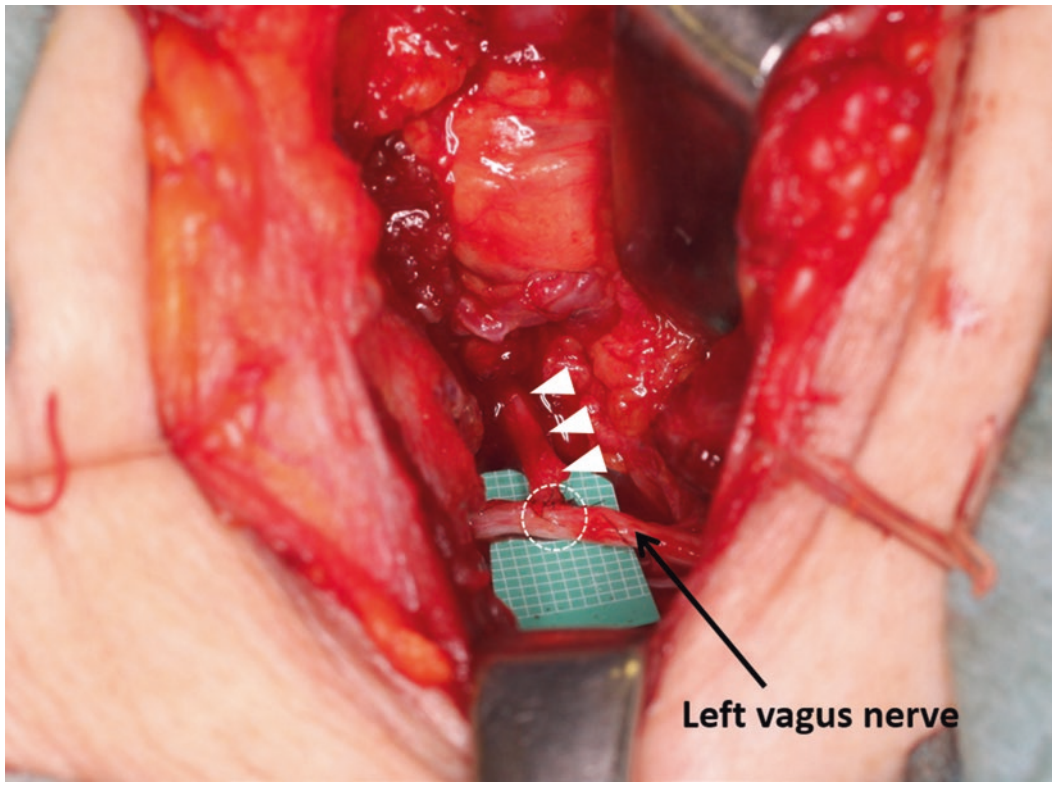

Fig. 2 Reconstruction of left recurrent laryngeal nerve. The end-to-side anastomosis between left recurrent laryngeal nerve and ipsilateral vagus nerve was performed under a microscope. Arrowheads were left recurrent nerve. Dotted circle indicated the anastomotic site between left recurrent laryngeal nerve and left vagus nerve

many adductors as abductor fibers in the recurrent laryngeal nerve; consequently, the reinnervated vocal cords are usually fixed at the median and the laryngeal muscle tone and mass can be restored.

Recurrent laryngeal nerve paralysis occurs during the dissection of lymph node along the recurrent laryngeal nerve. Therefore, careful surgical procedures are recommended to prevent recurrent laryngeal nerve paralysis. Surgeons should pay attention not to injure the recurrent laryngeal nerve by the intraoperative thermal damage, stretching, or compression of the nerve during esophagectomy. Recurrent laryngeal nerve reconstruction is a possible way to prevent the progressive loss of thyroarytenoid muscle tone and stiffness in the patient whose recurrent laryngeal nerve is resected together with metastatic nodes during esophagectomy.

4. Injury of thoracic duct

Thoracic duct may injure during esophagectomy, especially during mediastinal lymph node dissection. Chylothorax caused by injury to the thoracic duct can lead to a considerable loss of water and protein, with potentially serious effects on the respiratory and cardiovascular systems. The treatment of chylothorax is sometimes very difficult because it is not easy to find the injury point of thoracic duct. Careful surgical procedure along the thoracic duct should be recommended to prevent the injury of the thoracic duct.

During the development, thoracic duct first grows as two symmetrical tubes; numerous points of fusion between the two tubes occur and partly develop or disappear. The lower right part and upper left part remain and then connect. Finally, the thoracic duct forms as a single tube. Typically, the standard route of the thoracic duct is upward along the right side of the descending aorta and flowing into the left venous angle. However, there are many subtypes for its route. Based on these knowledge, intraoperative confirmation of the thoracic duct during esophagectomy is the most essential factor to avoid its injury. Between the esophagus and

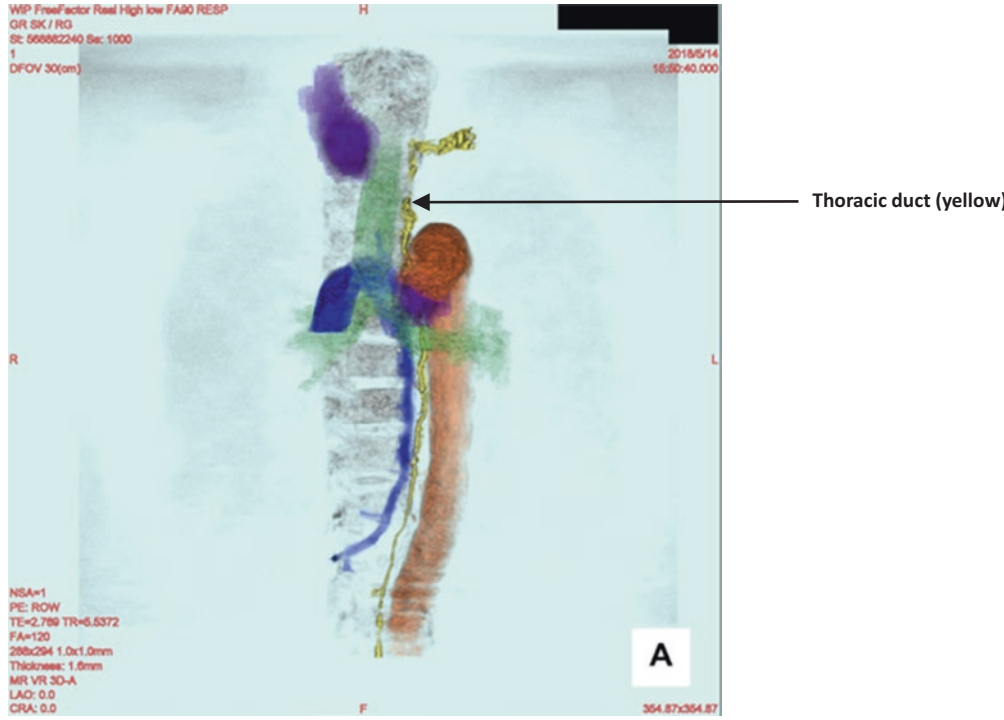

Fig. 3 Magnetic resonance thoracic ductography (anterior view)

thoracic duct, there are a number of communications, therefore, small lymphatic vessels have to be clipped or ligated reliably not to develop postoperative chylothorax.

Recent technology is advancing and can visualize thoracic duct preoperatively or intraoperatively. Magnetic resonance thoracic ductography prior to operation is feasible and can find out the thoracic duct in almost patients (Fig. 3) [11]. This method also can reveal the abnormality of the thoracic duct. Esophagectomy can be safely performed using this image as a guide. Intraoperative identification of thoracic duct using the fluorescence of indocyanine green is useful to prevent the injury of thoracic duct [12]. In the East Asia countries, thoracic duct is usually resected to complete the mediastinal lymph node dissection [13, 14]. So, intraoperative identification of thoracic duct is useful not only for prevention of postoperative chylothorax but also for maintaining the high accuracy of mediastinal lymph node dissection.

Summary

Intraoperative accidents and complications during esophagectomy cause serious and life-threatening conditions. Surgeons must understand the surgical anatomy prior to operation and must always consider the countermeasures for emergencies. Considering these life-threatening injuries, esophagectomy should be performed in an institute to be able to ask the help of cardiovascular surgeons. Once such horrible accidents and complications occur, surgeons are required to be calm and to recover the injuries by appropriate procedures.

Self-study

(1) Which injury does not usually occur during esophagectomy?
   (A) Tracheal vertical tear
   (B) Large tracheobronchial defect due to abscess
   (C) Bleeding from proper esophageal artery
   (D) Thermal injury of recurrent laryngeal nerve
   (E) Lymphatic leak from thoracic duct

(2) Which procedure is suitable to repair the intraoperative injury during esophagectomy?
   (A) Primary closure for tracheobronchial defect due to mediastinitis
   (B) Pedunculated dorsal muscle flap for pin-hole like tracheobronchial membrane injury
   (C) Clipping to the injury of right bronchial artery
   (D) Clipping to the injury of descending aorta
   (E) Sealing by electrocautery device to massive lymphatic leak after thoracic duct resection

Answer

(1) Which injury does not usually occur during esophagectomy?
   (A) Yes.
   (B) No (**Correct answer**).
   (C) Yes.
   (D) Yes.
   (E) Yes.

(2) Which procedure is suitable to repair the intraoperative injury during esophagectomy?
   (A) Pedunculated muscle flap is usually required to repair the tracheobronchial defect due to mediastinitis.
   (B) Primary closure and appropriate patch or flap using vital organs is suitable for pin-hole like tracheobronchial membrane injury.
   (C) Yes (**Correct answer**).
   (D) This method is impossible to repair the injury of descending aorta.
   (E) Suture or clipping of the thoracic duct may be necessary.

Conflict of Interest The authors have no potential conflicts of interest to disclosure.

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The Cervico-Thoracic Spine

Pınar Kuru Bektaşoğlu

Key Points

- Paravertebral tumours of the cervicothoracic junction are rare and anatomically challenging to excise lesions, comprising nerve sheath and primary bone tumours.
- Anterior medial neoplasms can be approached via anterior cervical approach combined with limited median sternotomy alone. Distal subclavian involvement mandates an anterior transsternal technique.
- Classification of cervicothoracic paravertebral neoplasms with mediastinal extension according to the their relationship with the subclavicular fossa allows for a structured surgical approach.
- Dual specialty involvement provides minimal morbidity and maximum resection with satisfactory oncological outcomes.

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Introduction

Cervicothoracic junction (CTJ) is defined as C7-T4 vertebras. Surgical treatment of pathologies in these region can be a challenging issue. Paravertebral neoplasms and infections of the cervicothoracic region extending into the apex, thoracic outlet and superior mediastinum are rare and their surgical treatment requires familiarity with the complex regional anatomy which is in the intersection of expertise of the spinal, thoracic and vascular surgeons. In particular, neurogenic tumours of brachial plexus or sympathetic chain origin as well as osseous/mesenchymal neoplasms mandate the involvement of a spinal surgeon with the relative expertise and are indeed part of a tertiary spinal department's practice (Fig. 1).

Several surgical approaches have been proposed, historically driven by thoracic surgeons aiming to resect apical lung carcinomas through extended thoracotomies. Approaches gradually expanded to other pathologies with less invasive and morbid techniques. Tumour resection through *anterior midline approaches* via *sternal division* have been described since the 1950s, but it was Birch and colleagues in 1990 who described a technique that managed to overcome the lateral limitations of the clavicle and sternocleidomastoid and widened the exposure [1]. The *anterior cervical transclavicular* (*Dartevelle*) *approach* popularised the anterior approaches with lateral extent to the thoracic

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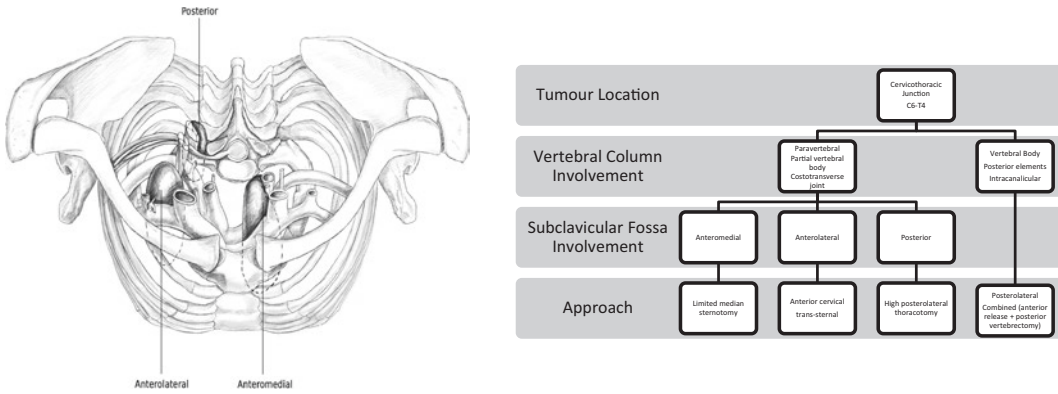

Fig. 1 Classification system and approach algorithm

outlet, but the clavicular division or even its modification with clavicle–sternal disarticulation led to deformities and mobility compromises. The *transmanubrial approach* that was advocated by Grunenwald and Spaggiari aimed at the osteomuscular integrity of the clavicle and shoulder. The same objective can be achieved with a *transsternal approach* via a limited upper sternotomy, while also preserving the first costal cartilage and not necessitating the transverse component of the incision, which form parts of the standard transmanubrial approach.

Despite the plethora of surgical approaches, there is a relative paucity in the literature regarding the surgical access choice and long-term outcomes of such lesions, as studies are understandably limited by a small number of patients and histologically heterogeneous cohorts. Varied approaches to the CTJ have been described in literature [low lateral anterior cervical approach (LACA), full sternotomy, lateral parascapular thoracotomy, clavicular dissection]. Among them, the low LACA combined with manubriotomy is the most used and safe approach.

Clinical Course

All cases are suggested to be discussed in a multidisciplinary forum and staging can be performed radiologically (whole body computer tomography (CT) and positron emission tomography (PET)), biochemically, clinically and through tissue sampling (CT-guided or intraoperative biopsy). Surgical strategies can be decided in advance through the shared case presentations and direct communication of two specialist teams led by an experienced spinal and thoracic surgeon. Procedures can be performed in either site, as appropriate facilities for both relevant extensive spinal and thoracic interventions are in place.

Indications for Surgery

Indications for anterior cervicothoracic approach includes biopsy, corpectomies or reconstruction of vertebral bodies for cancer, spinal cord decompression, fusion of vertebral bodies, scoliotic deformity correction, osteotomies, and infection in the cervicothoracic spine.

For pathological processes occurring in the anterior segment of the CTJ, LACA combined with manubriotomy can be used. The example for them are cervico-thoracic disc disease, vertebral osteomyelitis or discitis, fractures and tumors. The most recently published guidelines can be used to establish the need of a manubriotomy. Guidelines can be discerned based on magnetic resonance imaging (MRI) scans and CT scans:

(I) *MRI scan guidelines: based on T2 sagittal MR imaging at the midline including sternal manubrium. According to Teng guidelines, a line is drawn that starts from the suprasternal notch and extends horizontally*

to the corresponding anterior border of the vertebrae at the CTJ; another line that also starts from the suprasternal notch and extends posterosuperiorly to the midpoint of the anterior border of the C7/T1 intervertebral disc is drawn subsequently. The angle that meets at the suprasternal notch (SSN) is specified as the cervicothoracic angle (CTA). If the lesion is located above CTA (Type A), only LACA can be used. If the lesion is located within the CTA (Type B), LACA with manubriotomy can be used;

(II) *CT scan guidelines: based on sagittal CT scan reconstruction at the midline including the sternal manubrium. According to Karikari guidelines, the lowest accessible disc space that can be approached with LACA alone is determined by constructing a straight line passing through and parallel to the disc space that also passes above the manubrium (the intervertebral disc line). If the lesion is above this line, the manubriotomy is necessary. According to Falavigna guidelines, the superior healthy vertebrae are the first normal ones above the diseased levels in corpectomy cases, or the vertebra above the herniated intervertebral disc in microdiscectomy cases. The so-called "surgeons' view line" is defined as a line parallel to the inferior plateau of the superior healthy vertebrae and its correlation with the manubrium. If the surgeons' view line crosses below the manubrium, the manubriotomy is necessary.*

Tumors

Tumors can be classified according to subclavian fossa involvement as anteromedial, anterolateral, and posterior. Histopathological spectrum involves benign nerve sheath tumor, malignant bone or soft tissue tumors. The neurogenic tumours can be derived from the sympathetic chain or the caudal brachial plexus roots. Patient presentation includes painless neck mass, incidental finding on chest radiographs, neurology (Horner's syndrome or brachialgia) and finally surveillance imaging in neurofibromatosis patients. The malignant bone and soft tissue tumour group can consist of chondrosarcoma, osteosarcoma, leiomyosarcoma, liposarcoma, angiosarcoma, Ewing's tumour, plasmocytoma, thymoma and chordoma. The clinical presentation can consist of localised pain, local compressive symptoms (dysphagia, dyspnoea) or a result of surveillance imaging in cases of metastatic disease.

Preparation for Surgery

Before surgery, careful assessment of pulmonary and cardiac function is needed: clinical evaluation, pulmonary function tests including diffusing capacity of the lung for carbon monoxide (DLCO) and blood gas analysis. General anesthesia with endotracheal tube is the appropriate anesthetic approach. Radiolucent surgical table with ability to flex for added exposure is convenient if imaging for instrumentation is required. Neuromonitoring could also be helpful if there is neuropathologic involvement.

Position and Planes

Anterior cervical approaches are made in supine position. Because most pathological processes occur in the anterior segment of the vertebrae, the anterior approach is usually the best surgical option, allowing neural decompression, stabilization and restoration of anatomical spinal alignment. For LACA, the patient is positioned supine, the trunk 10° flexed and the head slightly rotated to the right. A roll pad can be placed under the shoulders to extend the cervical spine.

For thoracic pathologies, at the lateral decubitus position, move arm above patient's head. All pressure points should be supported with pads. Operating surgeon is positioned behind patient. If the pathology located at the right upper thoracic spine (T2-9), it is best approached from right side to avoid heart and aortic arch. If the pathology

is located on left thoracolumbar spine (T10-L2), it is best approached from left side to avoid liver retraction. There is no true internervous or intermuscular plane. Intramuscular dissection is through latissimus dorsi and serratus anterior.

Surgical Anatomy

It represents a big challenge for the spinal surgeon for the presence of important anatomical structures of the upper mediastinum: manubrium, thymus gland, left and right brachiocephalic veins (or innominate veins), right brachiocephalic artery, left common carotid artery, aortic arc, esophagus, trachea and thoracic duct. Specific anatomy should be reviewed before surgery in order to improve the success of the each intervention.

Approaches and Surgical Techniques

Access to CTJ can be done with *anterior cervical approach with extension to anterior chest wall*. *Open thoracotomy* is standard route to mid-thoracic and lower thoracic (T3-T10) region. *Transthoracic approach* to cervicothoracic spine allows excellent visualization and access to the anterior cervicothoracic spine.

- Cranio-caudal location between C6 and T4 vertebrae: more cranial lesions are conventionally approached by a *standard anterior cervical Smith Robinson incision*. Lesions with more caudal extent will most likely require *a thoracotomy*.
- Mediastinal extension: tumours with extension into the superior mediastinum (anterior and anterolateral) as lesions located in the posterior vertebral column or intracanalicularly can be accessed by *posterior or posterolateral approaches*.

Exposure to T3 can be achieved with an incision in the lower part of the neck with an extension to the anterior chest wall; however, anterior fixation is not possible in this incision. By extending the lower anterior neck incision to the anterior chest wall, the T2 vertebra is accessible and sternotomy is not necessary for exposure to T2. The anterior incision of the neck and limited sternotomy could create a narrow corridor (4-cm diameter) with limited exposure to the T3. In this regard, a modified version of Hodgson's technique by unilateral or bilateral manubriectomy (reserved T) in order to gain adequate access to the T5.

The other surgical routes are median sternotomy, anterior cervical transsternal approach, combined/modified transclavicular technique (Dartevelle), and high posterolateral thoracotomy. Here we will discuss some of the techniques in detail.

Manubriotomy

An incision is made on the left side along the anterior border of the sternocleidomastoid muscle and continued down the midline over the manubrium. The neck dissection is completed first. The sternomastoid, sternohyoid and sternothyroid muscles are sectioned. Then, manubriotomy is performed. A sternal saw is used to make a linear manubriotomy ending at the sternal angle to preserve the sternoclavicular joints, and a sternal retractor is applied. Dissection proceeds with thymus gland resection. The left anonymous vein and the brachiocephalic artery are isolated and gently right-downward retracted using vascular loops. An anterior cervical fusion retractor is positioned allowing exposure of the lower cervical region to the upper thoracic spine. Microdiscectomy, single or multiple corpectomies, tumor resection can be performed. At the end, reconstruction with cages and anterior plating can be assessed with anteroposterior and lateral X-ray scan. A suction drain is left in the prevertebral space and substernal plane. The manubrium is reapproximated with flexible steel wires and the suture completed.

Transthoracic Approach to Thoracic Spine

A curve incision starting halfway up the medial border of the scapula halfway between the scapula and thoracic spine, down to a point two fingerbreadths below the tip of scapula is performed for thoracic pathologies. The incision is finished by curving upwards towards the inframammary crease.

At the superficial dissection step, divide latissimus dorsi in the direction of the incision, divide the serratus anterior along the same line to the ribs, and enter the chest via intercostal space or rib resection. *Ribs resection approach* offers greater exposure and bone for autograft. For *intercostal approach* use 5th intercostal space for pathology from upper thoracic spine to T10 and use 6th intercostal space from T10 and lower. For cutting the periosteum on upper border of rib, entering on upper border of rib protects intercostal nerve and vessels. After entering the pleura, resect posterior three fourths of the rib for added exposure and insert rib spreader.

At the deep dissection step, deflate the lung and retract lung anteriorly with moist lap sponge. Incise pleura over lateral esophagus to allow for retraction of esophagus, retract esophagus anteriorly, tie off as few intercostal vessels as possible, and reflect periosteum over spine with elevators to expose involved vertebrae.

Postoperative Management

In the post-operative period intensive care is not routinely recommended.

Effective analgesia is an essential part of postoperative management. Important injectable drugs for pain are the opiate analgesics in the first 2 days. Nonsteroidal antiinflammatory drugs, such as diclofenac (1 mg/kg) and ibuprofen can also be given orally as can paracetamol (15 mg/kg) for the next 7–10 days.

Infections prophylaxis consisting in 3 g Amoxicillin for 7 days is recommended in all cases. Low molecular-weight heparin and compression stockings for thrombo-embolic prophylaxis are mandatory until the complete mobilization of the patient.

The patient usually starts the mobilization on the 3rd postoperative day. The surgical drain can be removed after 48–72 hours. A cervical orthosis such as a Philadelphia collar must be used for 3 months for cervical cases. X-ray scan after the mobilization of the patient is recommended.

Intraoperative Accidents and Complications

For LACA combined with manubriotomy, dysphagia and dysphonia are the most common complications and are usually transient conditions. They can begin in the immediate postoperative period. Dysphagia can be treated protecting the airway with postural adjustments to reduce risk of aspiration, doing exercises to strengthen weak facial muscles, to improve range of oral or pharyngeal structural movement, and/or to improve coordination.

Intercostal vessels are vulnerable during rib resection when running along undersurface of rib, and exposure of vertebrae within chest. Careful attention should be given in order to avoid injury by entering pleura from above the ribs. Avoid lung injury by using sharp instruments wisely when within chest, and expand lungs every 30 minutes to prevent microatelectasis. Avoid injury through adequate retraction of esophagus while working on spine. Artery of Adamkiewicz, travels on left side between T9-L2 in 60% of patients, must be preserved to prevent spinal cord ischemia. Other complications are Horner's syndrome, infection, and transient neurological deficit. It is important to preserve recurrent laryngeal nerve, gullet and thoracic duct.

Infections may include skin infections, spondylodiscitis and osteomyelitis. Sternal osteomyelitis and mediastinal infection following manubriotomy may be effectively managed through rigorous debridement of infected soft tissues, resection of the damaged sternal segment and adequate postoperative drainage.

Pearls and Pitfalls

The LACA combined with manubriotomy allows extensile exposure of the CTJ and is associated to a low rate of complications. Age and body mass index are major determinants of accessibility, followed by neck shape (long neck vs. short neck). In most of cases this approach allows a complete access from C3 to T3. The exposure of T4 in many cases is less adequate because the space is narrow and deep. For T4–T5 level is generally recommended a right thoracotomy. A left side approach is preferred to minimize the risks of recurrent nerve injury. The recurrent laryngeal nerve on the left side has a longer route and has a relatively fixed anatomy in the tracheoesophageal groove while on the right side it presents substantial anatomical variations.

Conclusions/Summary

Cooperation of thoracic and neurosurgeons improve the surgical exposure and prevent probable complications in complex cervicothoracic spine pathologies.

Self-study
Which of the following approach is not prefered for cervicothoracic junction pathologies?

(A) Low lateral anterior cervical approach
(B) Full sternotomy
(C) Lateral parascapular thoracotomy
(D) Clavicular dissection
(E) Abramson procedure

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https://www.orthobullets.com/approaches/2079/transthoracic-approach-to-thoracic-spine

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The Superior Thoracic Aperture

Pınar Kuru Bektaşoğlu

Key Points

- Thoracic outlet syndrome (TOS) is best thought of as two separate conditions, depending on the structure causing the symptoms: neurogenic TOS (nTOS) and vascular TOS (vTOS).
- Although the main cornerstones of diagnosis are the patient's presenting history and physical examination, imaging studies can be helpful to confirm the diagnosis or site of involvement, delineate abnormal anatomy, evaluate for other potential causes of the patient's symptoms, and appropriately classify the patient's condition as nTOS, and vTOS.
- It is critically important to recognize that the diagnosis of vTOS is not made by identifying positional changes in the vessel caliber alone. Both symptomatic and asymptomatic patients can have arterial and/or venous compression at the thoracic outlet at cross-sectional imaging. Venous compression is much more common, and occurs in over 50% of asymptomatic patients.
- Magnetic Resonance Imaging (MRI) is the noninvasive cross-sectional imaging test of choice in patients with suspected TOS. Given that the evaluation for positional narrowing requires imaging acquisitions in multiple positions, MRI has an inherent advantage over CT due to its lack of ionizing radiation, an advantage of particular benefit in the generally young patient population affected by TOS.

Introduction

The superior thoracic aperture, also known as the thoracic inlet or outlet, connects the root of the neck with the thorax. TOS is characterized by compression of the brachial plexus and/or subclavian vessels as the structures pass through thoracic outlet to the axilla. Sir Astley Cooper, English surgeon and anatomist, first described the symptoms attributed to TOS in 1818. Bramwell (1903) recognized the first rib as the cause of TOS. Peet et al. (1956) coined the term "thoracic outlet syndrome". There have been always a disagreement about the clinical relevance and pathology of TOS throughout the history and there still no golden standard for diagnosis and treatment of TOS.

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There is mainly two types of TOS: neurogenic and vascular.

1. Neurogenic TOS (nTOS) is more common (approximately 95%), and caused by the compression of the brachial plexus. nTOS involves compromise of the brachial plexus trunks or cords formed from nerves that come from the C5 to T1 spinal levels. Commonly, lower trunk of the brachial plexus is involved. In diagnostic work-up of nTOS, electrophysiological nerve studies and anterior scalene muscle (ASM) blocks give insight about patients likely to benefit from surgical decompression of TOS.
2. Vascular TOS (vTOS) generally involves vessel compression (mostly subclavian artery and vein), or venous thrombus formation could also result in vTOS. Variations in the insertion of the ASM or scalenus minimus muscle, the presence of a cervical rib or fibrous and muscular bands, variations in insertion of pectoralis minor, and the presence of neurovascular structures, which follow an atypical course are common anomalies encountered in TOS. The preferred diagnostic modality for vTOS is duplex imaging.

One of the pioneer surgical interventions for decompressing TOS symptoms is resection of the first rib. Thomas Murphy was the first who documented a procedure involving excision of the first rib and reported significant decompression of TOS in 1910. The transaxillary approach is the most common and successful technique for decompression of TOS. It allows the greatest exposure for first rib excision to relieve compressed vessels. Alternatively, a supraclavicular approach is preferred for scalenotomies when the ASM impinges on surrounding structures. It is indicated for compression of the median nerve distribution. A combined supraclavicular and infraclavicular approach is preferred for vTOS involving a cervical rib or large cervical vertebral transverse process when a larger surgical exposure is needed. In the management of TOS, improved diagnostic and treatment techniques, and the developed consensus gold standard for diagnosis are needed. Three-dimensional view of the thoracic outlet is obtained with helical computed tomography (CT), and anatomical variations which may predispose patients to TOS may be detected with this modality. This chapter covers the clinical and anatomical presentations of TOS, and the diagnostic and treatment techniques for the condition.

Etiology of Thoracic Outlet Syndrome

Thoracic outlet syndrome, is mainly caused by dynamic compression which is exacerbated by postural changes and effected by anatomical variations or pathologies (abnormalities of first rib, anomalous muscles or muscular insertions, cervical ribs, elongated cervical transverse processes, fibrous bands, etc.) and trauma related changes. The mechanism of compression is often not easy to identify; in addition to the presence of a cervical rib, alterations of the costoclavicular ligament and anomalies of the scalene muscles have been identified as common factors in the etiology.

It is thought that in vTOS, the thrombosis occurs because there has been an intrinsic narrowing of the subclavian vein caused by compression and scar tissue, which has formed as a result of repetitive compression injury to the subclavian vein between the clavicle and first rib. The thrombosis formation is the secondary process.

Clinical Presentation of Thoracic Outlet Syndrome

A young, thin female with a long neck and drooping shoulders, who complaints chronic pain in the neck or shoulder and paresthesias in the medial aspect of the arm and hand is the picture of a typical patient with TOS. Chronic nerve compression is rarely the case. Gilliatt–Sumner hand is one of the classic findings of true nTOS, which is characterized by severe atrophy of the abductor pollicis brevis muscle,

as well as less severe atrophy of the interosseous and hypothenar muscles of the ipsilateral side.

There are four tests for the physical examination of TOS. They are Adson or scalene test, the Halstead maneuver, Wright hyperabduction maneuver, and Roos test. The tests are not specific nor sensitive for TOS. Warrens and Heaton concluded that 58% of random volunteers had at least one positive test result. There is a wide variations of symptoms and nonspecific nature of TOS, especially in the elderly and female patients differential diagnosis must include cardiac, pulmonary, traumatic or degenerative cervical spine, and distal neuropathic etiologies [4].

An arterial TOS generally caused by compression of the subclavian artery in patients with a history of strenuous arm activity above the head, and probably present with the typical signs and symptoms of ischemia (i.e. pain, pallor, paresthesia, pulselessness, and extremity poikilothermia). Cervical rib or other bony abnormality is a frequently reported findings in these individuals. Acute thrombosis of the subclavian and axillary veins in young men after vigourous exercise often cause venous TOS. Pain, edema, and cyanosis complaints are diagnostic in these cases. In chronic venous thrombosis, extensive collateral circulation may seen. However, many cases are intermittent in nature. Duplex ultrasound aid the diagnosis of vTOS, which has been found to be 92% sensitive and 95% specific. Although vascular etiologies represent fewer than 5% of TOS cases, in true vascular compromise surgery is indicated.

Anatomy of Thoracic Outlet

Understanding the anatomy and compartments of the thoracic outlet is essential for accurate reporting of the location of disease. The superior thoracic aperture is kidney-shaped and lies in an oblique transverse plane, tilted anteroinferiorly to posterosuperiorly. The thoracic outlet extends from the cervical spine and superior border of the mediastinum to the lateral border of the pectoralis minor muscle. Boundaries of superior thoracic aperture are posteriorly, T1 vertebral body and costovertebral joints; laterally, first ribs and their costal cartilages; anteriorly, superior border of the manubrium.

Below listed structures are the major structures that pass through the superior thoracic outlet:

- Viscera: thymus, trachea, esophagus, lung apices
- Vessels, nerves and lymphatics: common carotid arteries, subclavian arteries, confluences of internal jugular and subclavian veins, phrenic nerves, vagus nerves, recurrent laryngeal nerves, thoracic duct, sympathetic trunk, prevertebral fascia
- Muscles: sternohyoid muscle, sternothyroid muscle.

Anatomically, the thoracic outlet can be divided into three compartments [4]

1. The most medial compartment, **the scalene triangle**, lies above and behind the clavicle. The scalene triangle is bordered by the middle scalene muscle posteriorly, the ASM anteriorly, and the first rib inferiorly. The scalene triangle contains only the subclavian artery and brachial plexus; as the subclavian vein lies anterior to the ASM, it is thus outside the triangle.
2. Moving laterally, **the costoclavicular space** (cervicoaxillary canal) is bordered by the subclavius muscle anteriorly, the clavicle superiorly, and the first rib and ASM inferiorly and posteriorly. The costoclavicular space contains the entire neurovascular bundle.
3. The most lateral compartment of the thoracic outlet lies inferior to the clavicle and is known as **the subcoracoid pectoralis minor space**. In the pectoralis minor space, the neurovascular bundle courses between the pectoralis minor muscle tendon anteriorly and the ribs and intercostal muscles posteriorly.

The anatomy of the thoracic outlet is dynamic, with abduction of the ipsilateral arm potentially resulting in narrowing of the thoracic outlet at all three spaces. This narrowing can be seen in

symptomatic and asymptomatic patients and plays a role in development of neurovascular compression in patients with TOS.

Diagnostic Work-up for Thoracic Outlet Syndrome

One of the challenges faced with TOS is the lack of definitive diagnostic modality.

Computed Tomography

Multidetector (161) CT (MDCT) scanning is a technique recently used in visualization of the thoracic outlet with ability to do 3D reconstruction of the anatomy, including bone detail. Prior to the development of MDCT, CT images could only be viewed in the transverse plane. In 1997 Matsumura et al. reported the potential diagnostic application of MDCT by observing impingement on the subclavian artery and vein in a number of arm positions. MDCT may increase the efficacy of TOS diagnosis for each type of TOS, as this procedure offers a more complete view of the thoracic outlet.

Magnetic Resonance Imaging

Magnetic resonance imaging is useful for the detection of cervical ribs and fibrous bands. It is also helpful in identifying potential causative factors of TOS and individual anatomical variations that could lead to TOS.

Three-dimensional contrast-enhanced magnetic resonance angiography (3DCE MRA) has recently been developed for diagnosing vascular complications resulting from TOS. It is an excellent technique for obtaining images of the brachial plexus, aortic arch and vessels of the upper extremity. Because of this, it has gained support for utilization as a potential diagnostic approach for the demonstration of vascular compression as a result of TOS. In comparison with two-dimensional time of flight (2D TOF), 3DCE MRA provides far better vessel visualization and identifies the underlying cause of TOS, particularly when the arm is in extended position. Through improved localization of vascular compression with 3DCE MRA, surgical intervention could be more precise in comparison with alternative diagnostic approaches.

Other Imaging Studies

- **Conventional Angiography**

When vTOS is suspected, conventional angiography is the mainstay for the diagnosis of arterial TOS.

- **Computed Tomography Angiography**

Computed tomography angiography is the most common imaging study to diagnose and plan the treatment of patients with vTOS.

- **Venography**

Venography is used for thrombus formation [4].

- **Duplex ultrasound imaging**

Duplex ultrasound imaging is a noninvasive, cheap method that could identify stenosis and vascular compression associated with TOS, and is associated with both high-sensitivity and high-specificity results in the diagnosis of vTOS. When combined with Adson test, the false positive response is nearly 0%. This modality is preferred to angiography and venography in diagnosing vTOS.

Nerve Conduction Studies

The only reliable objective test is a measured reduction in nerve conduction velocity across the affected nerves to a value less than 85 m/s beyond the physical signs. In advanced cases of nTOS, common observations include decreased sensory potential along the ulnar nerve and decreased compound motor potential along the median nerve. This is an effective way to differentiate the patients suitable for surgical

decompression of nTOS. The medial antebrachial cutaneous nerve conduction velocity may be a sensitive way to detect pathology in the lower trunks of the brachial plexus which is promising for future research.

Anterior Scalene Muscle Blocks

Direct ASM blocks would relieve muscular tension and would guide clinician for the patients who could potentially benefit from decompressive surgery. This makes ASM blocks a screening tool for selecting candidates for decompression surgery.

Non-surgical Treatment Strategies for Thoracic Outlet Syndrome

Conservative treatment with pharmacotherapy and physiotherapy directed at postural and strengthening of the shoulder girdle to relieve tension on the brachial plexus can be preferred in patients with nTOS. Botulinum toxin injection has also been used for treatment of nTOS [2], and Torriani et al. reported their measure to provide symptomatic improvement of nTOS complaints in 69% of the 41 patients receiving injections in the ASM, pectoralis minor, or subclavius muscle.

Surgical Techniques for Thoracic Outlet Syndrome

In patients with vTOS and patients with nTOS with unresolved symptoms, surgical treatment is the management of choice [1]. One of the oldest surgical interventions for decompressing TOS symptoms is removal of the first rib. First documented in 1910 by Thomas Murphy, a procedure involving excision of the first rib provided significant decompression of TOS.

Timing of surgery for patients with TOS is controversial but typically follows a course of postural exercises as supervised by an experienced physical therapist. Early surgery is recommended for those patients with confirmed nTOS or vTOS.

Supraclavicular: Scalenotomy, Scalenectomy, Neurolysis, ±First Rib Resection

If the first rib is the causative factor, first rib resection with a scalenectomy, followed by a postoperative venogram and anticoagulation is recommended. However, this method is a less appropriate approach for the resection of the first rib because of the difficulty in visualization of the structure.

Scalenotomy

Under general anaesthesia a patient is prone positioned. Under the shoulders a flat roller is placed. The neck is gently reclined and turned to the opposite side of the operated one. The incision is performed ~2 cm above the clavicle. The medial limit of the incision is the sternocleidomastoideus (SCM) muscle. The length of incision is typically 4–6 cm. Attempts are made to preserve and retract the external jugular vein by a blunt hook while separating the layers. The lateral limit of SCM muscle may be slightly incised at the collarbone, thus forming additional space towards the scalene muscles. After reaching the inferior belly of the omohyoideus muscle, the muscle is slightly mobilised in both sides and pushed in the superolateral direction by a blunt hook. Having retracted the omohyoid muscle, it is usually easy to palp the ASM between the omohyoid muscle and the SCM muscle. The transversus coli vein, which is usually found in this area, can be safely ligated or retracted.

Having visualised the ASM, it is necessary to separate its lower surface from subclavian artery and vein. Then, the muscle can be safely cut by performing bipolar haemostasis. While cutting the muscle, strong fibrotic fibres can often be felt, which, supposedly, could be the cause of the symptoms. When the muscle is separated and the brachial plexus and major blood vessels are exposed, it is necessary to examine and palp with a finger the area of the plexus, because frequently, separate fibrotic strands are found around the muscle, which can also cause the disease, and thus, they also should be cut. After the surgery, an active drain is left in all the cases.

Transaxillary: First Rib Resection

This method is preferred for vTOS. The transaxillary first rib resection is a much more complicated intervention than incision or resection of the scalene muscle, thus increasing the surgical risk to the patient. The surgery can damage the nerve plexus and the long thoracic or phrenic nerve, and pleural injuries may cause haemothorax (more often due to the subclavian vein trauma), pneumothorax and chylothorax. The recovery and rehabilitation period until returning to work lasts for at least a month. If resection was incomplete and a part of a rib was left, the scalene muscles can reattach to it (Figs. 1 and 2).

Combined Supraclavicular and Transaxillary

Posterior: Affords Proximal Exposure to C8 and T1 Nerve Roots; Especially Useful for Revision TOS Cases

This method is the technically most demanding one because of the need for traversing the suspensory muscles of the scapula, potentially related with complications. However, this method provide good visual field of the lower trunk of the brachial plexus. This modality can be preferred in situations that method described above do not resolve the complaints' of the patients with TOS. This approach could

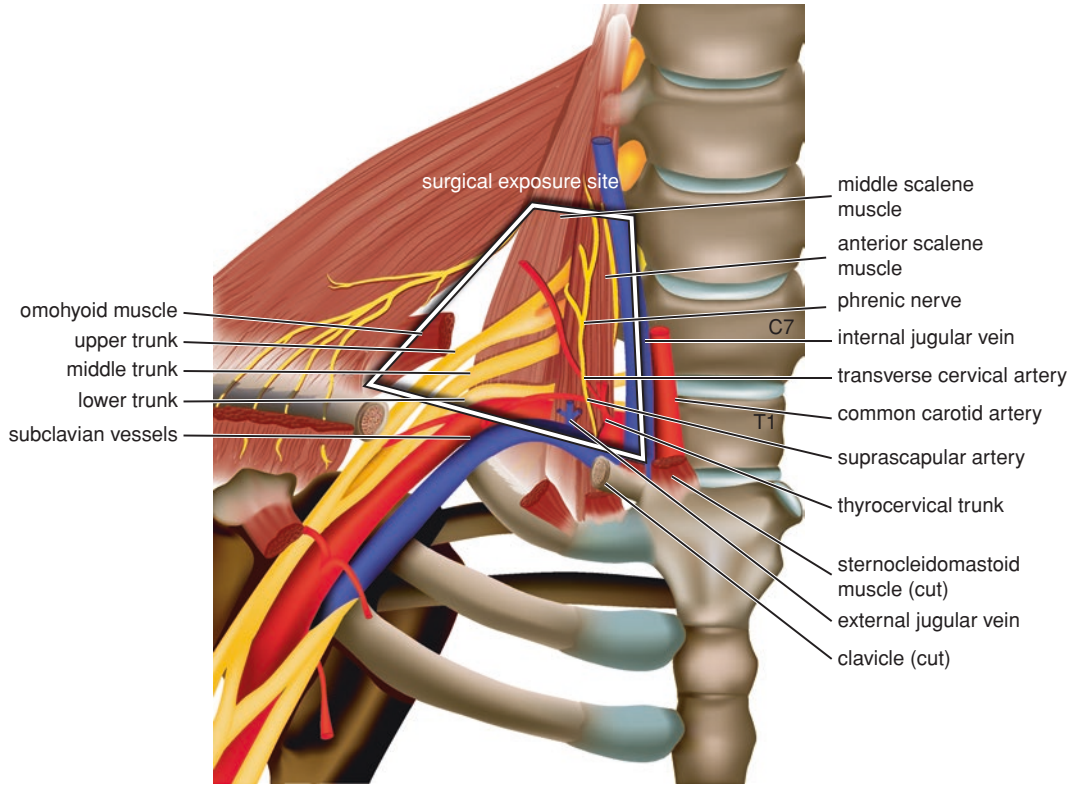

Fig. 1 An illustration of the relevant neurovascular anatomy in anterior supraclavicular neurosurgical approach to the brachial plexus and subclavian vessels for thoracic outlet syndrome. Nicholas Zaorsky, M. D. obtained from (date: 01.05.2019): https://en.wikipedia.org/wiki/Thoracic_outlet_syndrome

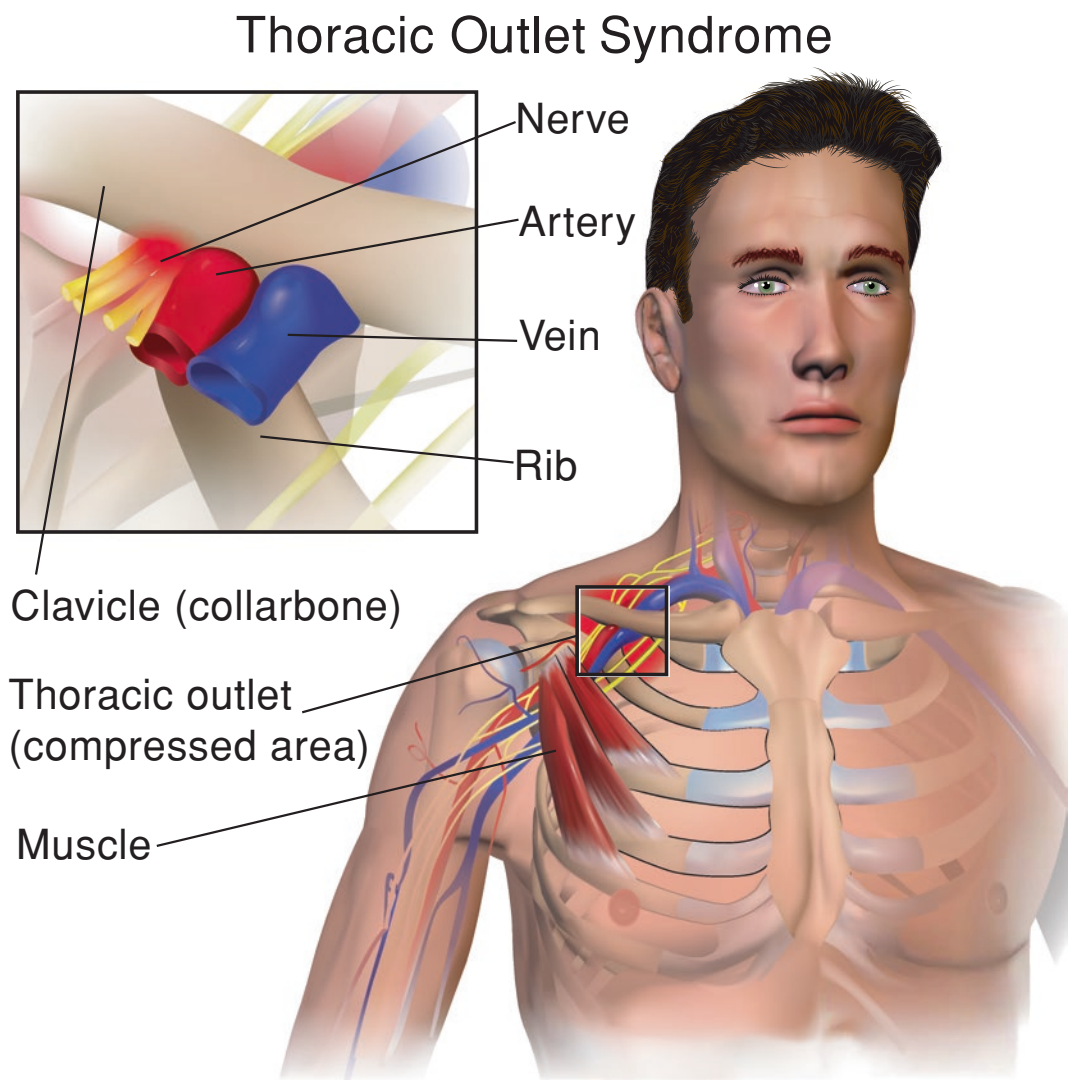

Fig. 2 Demonstrative figure for thoracic outlet syndrome. Bruce Blaus obtained from (date: 01.05.2019): https://en.wikipedia.org/wiki/Thoracic_outlet_syndrome

also be completed with concomitant dorsal sympathectomy.

Recent Development in the Management of Thoracic Outlet Syndrome

The expanding field of minimally invasive surgery has also impacted the treatment of TOS. In 2005, Martinez et al. reported that they used the robotic da Vinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA) to improve visualization during transaxillary rib resection with no mortalities or permanent neurovascular injuries. In 2007, Abdellaoui et al. described an endoscopic technique for improved intrathoracic visualization, by making a 6–7 cm axillary incision and introducing a camera and instruments through the incision. Endoscopic management of TOS improves identification and dissection of the neurovascular bundle. Furthermore, percutaneous angioplasty has been used in conjunction with thoracic outlet

decompression to treat subclavian vein compression because of TOS. In 2004, Schneider et al. reported patients with residual subclavian vein compression, and reported a technical success rate of 100% with treatment involving intraoperative percutaneous angioplasty. Kara et al. [3] reported different minimal invasive method, that they reached the first rib through the axillary incision rather than the pleural cavity which prevents the need for a postoperative drain placement and may reduce the duration of hospitalization. Kocher et al. [5] developed transthoracic, robotic assisted approach using the DaVinci console for TOS and first rib resection.

Intraoperative Accidents and Complications

Injury to the Phrenic Nerve

The phrenic nerve (diaphragm nerve) should be carefully identified. Typically, it lies on the surface of ASM and can be easily preserved by visualising it and passing a silicone sling around it, but the position of the nerve can vary considerably. Moreover, there is a possibility of an extra phrenic nerve, and therefore, it is always necessary to make sure that the nerve is in a safe position. Such injuries may be temporary or permanent with presenting features of shortness of breath on exertion and impaired exercise tolerance. If patients are on a ventilator then there may be difficulty in weaning of ventilator. X-ray shows elevation of the affected hemidiaphragm. This is confirmed by ultrasound or fluoroscopy, which is the diagnostic study of choice in evaluation of these injuries. The best method of management of unilateral palsy is diaphragmatic plication.

Lymphorrhoea

One should keep in mind that this neck area is full of lymphatic vessels, which, if damaged, may result in lymphorrhoea, and therefore, careful dissection is necessary.

Pleural Effusion or Pneumothorax

Many surgeons will intentionally violate the apical pleura to provide a means for decompression of postoperative fluid into the pleural space. Thus, small or even moderate pleural effusions or a small pneumothorax are not unexpected findings.

The Future of TOS

The future of TOS will likely revolve around improving diagnostic procedures and criteria, as well as the continued improvement of treatment techniques. The value of conservative management in the form of physical therapy regimens should not be overlooked, yet definitive treatment of TOS generally relies on surgical intervention to yield optimal patient relief and satisfaction. Surgeons should be competent in identifying symptoms related to TOS, even though diagnosis remains difficult because of the subjective variability of presenting symptoms and patient complaints. Greater emphasis on diagnostic evaluation will lead to improved treatment outcomes for those suffering from TOS.

Conclusions/Summary

Thoracic outlet syndrome is a clinical diagnosis and there is still room for optimal diagnosis and treatment. In cases with refractory symptoms despite conservative treatment, surgical alternatives can be considered. Recent advances in imaging techniques aid the diagnosis. There is promising advancements in minimal invasive TOS surgery via robot assisted.

Self-study

1. **In which of the below diagnostic test does not related to thoracic outlet syndrome?**
   (A) Adson test
   (B) Halstead maneuver
   (C) Wright hyperabduction maneuver
   (D) Roos test
   (E) Phalen's test

2. **In which of the below compartment does not belong to thoracic outlet?**
   (A) Subcoracoid pectoralis minor space
   (B) Costoclavicular space
   (C) Cubital tunnel
   (D) Scalene triangle

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Surgical Techniques for Chest Wall Diseases

Marco Scarci, Benedetta Bedetti, Luca Bertolaccini, Davide Patrini, Joachim Schmidt, Fabrizio Minervini, and Piergiorgio Solli

Key Points

- Chest wall diseases include a broad range of pathologies, which are oft treated with different surgical techniques
- The surgical treatment of pectus excavatum is indicated when patients are symptomatic. In this case, two options are possible: the open approach by Ravitch or the minimally invasive Nuss operation
- Chest wall traumas require surgical treatment in case of flail chest or instable sternal fractures
- The surgical management of chest wall neoplastic diseases depends on the primary tumor.

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Introduction

There is a broad spectrum of pathologies that can affect the chest wall and we can divide them in 3 main groups: congenital malformations, traumatic injuries and neoplastic diseases. In general, chest wall resections and reconstructions for neoplastic or non-neoplastic diseases are always a great challenge. In this chapter we will describe the most common surgical techniques of resection and reconstruction.

Congenital Malformations

Pectus excavatum is the most common congenital malformation of the chest wall. It is characterized by a depression of the sternum and the costal cartilage and represents nearly 90% of chest wall defects (Fig. 1) [1]. Pectus carinatum is characterized by an anterior convex protrusion of the chest wall and it is the second common chest wall deformity (Fig. 2) [2].

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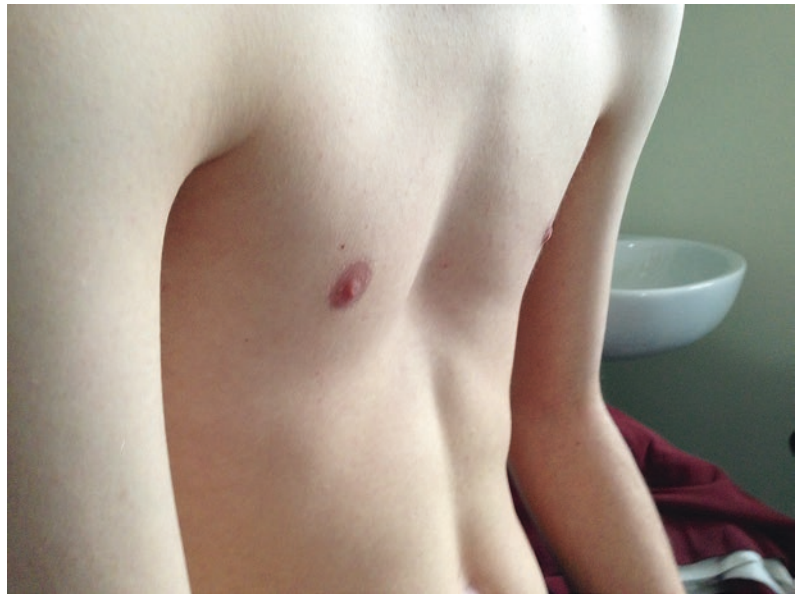

Fig. 1 Typical features of pectus excavatum

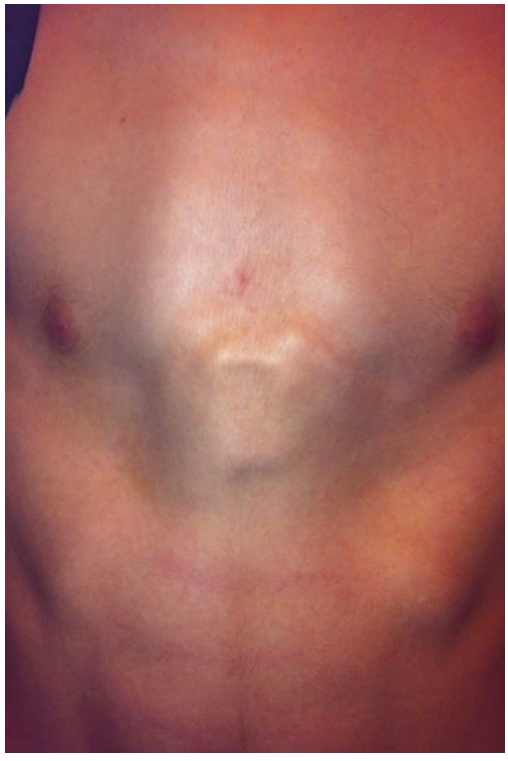

Fig. 2 Typical features of pectus carinatum

These malformations are visible from the infancy or adolescence and often the psychological burden is as important as the physical limitations.

a. **Surgical therapy for Pectus excavatum**
Indications for surgery are symptomatic patients with a Haller Index >3.5 [3]. Dyspnea on exertion and pain are typical symptoms in young patients. The preoperative work up should include a psychological assessment and an echocardiography, in which often is seen the compression of the heart through the sternum [4]. There are classically two main operative techniques for pectus excavatus repair: the open [5, 6] and the minimally invasive technique [7, 8], which will be illustrated in the next paragraphs.

a.1. **Open Repair of Pectus Excavatum (modified Ravitch Repair)**
The patient is positioned supine on the operating table. To start, a transverse, inframammary skin incision at the level of the deepest part of the sternal defect is performed. There is much debate on whether to perform the

incision vertically on top of the sternum or along the mammary creases to get a more cosmetic result. In our opinion the best approach is to make a short, less than 10 cm, incision vertically and then to use a soft tissue spreader, like an Alexis, to move around the soft tissues. We believe that to achieve a good correction through an horizontal incision requires too much dissection of soft tissues with potential for seroma formation and hematomas. Then the skin and the pectoralis major muscle are elevated to expose the sternal malformation comprehending sternum and costal cartilages. To achieve a god closure of the wound at the end of the procedure, without retraction of the skin, it is important to slightly detach the skin and derma from the underlying muscle for about 1 cm laterally on both sides. For this manouvre we recommend to use the cut function of the diathermy rather than the cautery, to avoid tissue damage and fusion of the planes.

The next step is the subperichondrial resection of the abnormal costal cartilage without touching the perichondrial sheath. This will permit the mobilization of the sternum in the right position and the sheath will take part in the rib regeneration after the surgery. The subperichondrial resection is performed incising the perichondrium starting from the chondrosternal junction medially and then the perichondrium is dissected away from the cartilage. The right plane of dissection is the avascular area between perichondrium and costal cartilage. The perichondrium is dissected until the exposure of the posterior part of the costal cartilage. We prefer a trap-door incision of the cartilage using a sharp 11 blade. This allows a circumferential dissection of the perichondrium without damaging it. Afterward it is possible to use the excess tissue for plication to reinforce the repair. The cartilage is lifted with an elevator and then incised with a scalpel and removed. Generally the costal cartilage is removed from the ribs 3 to seven bilaterally, but this can vary in some patients. After this, usually two wedge osteotomies are performed on the sternum to compensate for the sternal deformity. One is performed at the level of the most depressed part of the deformity and the other one, lower down, at the level of the most elevated one. The superior incision is filled with bone growth accelerator and pieces of the removed cartilages to create a scaffolding for new bone formation. It is eventually stabilized with reabsorbable plates in younger patients or titanium one is older ones. The lower incision is then approximated with number 1 nylon sutures. Finally subcutaneous drains are inserted and the skin incison is closed.

a.2 **The minimally invasive technique: The Nuss procedure**

The patient is placed supine with the right arm elevated at 90° on a support, the pulsoxymeter is placed on the finger of the right hand to make sure there is no ischemia during the procedure. The left arm is stretched out on an arm board.

Two small incisions are then performed on each side of the thorax lateral to the deepest part of the defect. Then a subcutaneous dissection is performed above the fascia of the serratus muscle on both sides until about 1–2 cm from the sternal edge. An additional port for the scope is placed below the skin incision on the right side, usually on the 5th intercostal space.

The defect is the measured and than the bar is adapted with the bar bender to the patient's chest. In some cases there is the need to insert a second bar one or two intercostal space above to correct the defect. A 30° thoracoscope is then used to inspect the chest. Entrance into the chest is achieved with a the pectus introducer medially to the highest point of the depression. The introducer is then rotated by 180 degree and advanced below the sternum, from right to left, always maintaining contact with the chest wall. In deep defect we use to place a bar to partially elevate the sternum and use a trans-esophageal echo to assess the left side. Seldom bilateral thoracoscopy can be used.

Once the introducer is on the other side the exit point is again medial to the highest point of the defect. It is important to push up rather than laterally to avoid stripping the intercostal muscle. A nylon tape is then tied to the tip of the introducer and the bar to the nylon tape, leaving less than a 1 cm gap between the tip of the introducer and the bar. This allows avoiding

the retraction of the soft tissues once the introducer is removed and facilitate the passage of the bar. Especially using a serrated bar there is a risk of damaging the intercostal vessels which is reduced with this technique.

The bar is tied to the tape and place through the chest with the convex side posteriorly from the right to the left side under vision. After the bar is located behind the sternum, in can be rotated 180° using the bar flippers, placing them at the end of the bar. This maneuver allows the sternum to be pushed anteriorly, correcting the defect. Before turning the bar it is recommended to use the table bender to make sure that both ends of the bar are flushes to the muscles. Also make sure that the stabilizers can slide on the bar and it is not to bent.

Then stabilizing bars are placed to secure the end of the bars. Finally a chest tube is placed of the right side and the skin incisions are closed. Subcutaneous drains can be placed, if needed (Fig. 3).

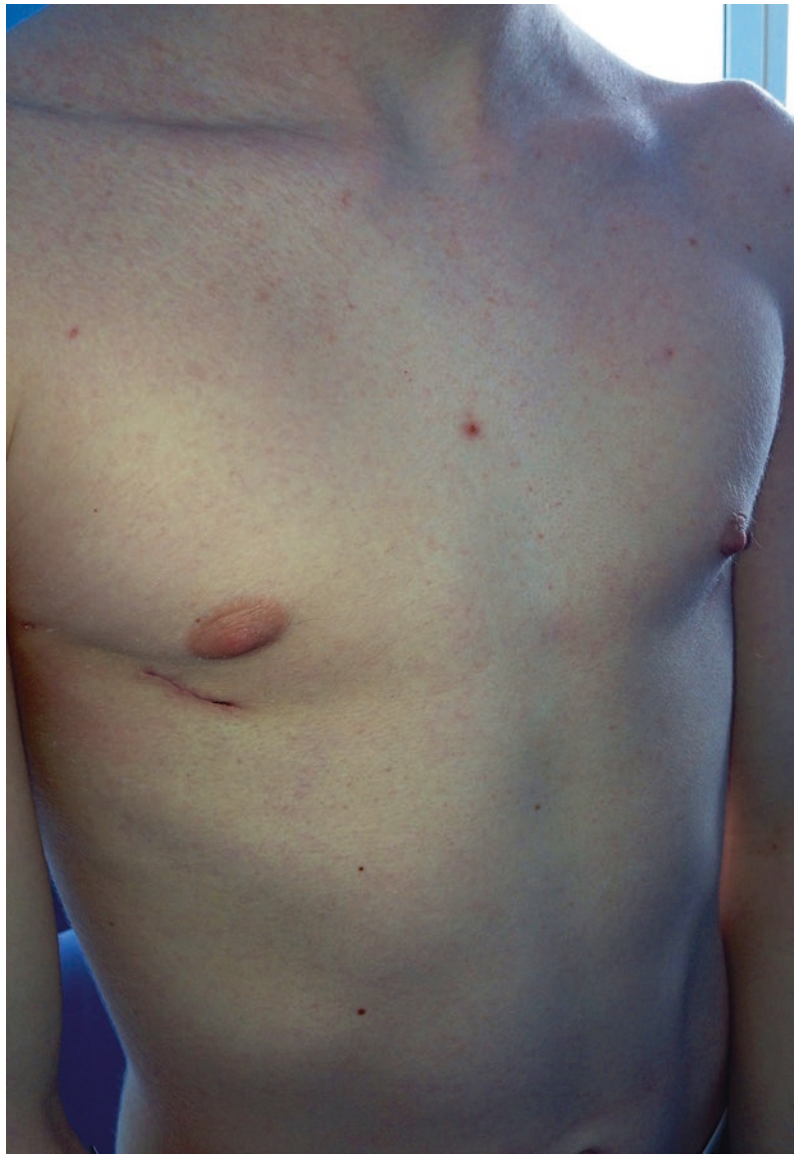

Fig. 3 Patient with pectus excavatum after surgery

The pectus bar should be removed in 2–3 years.

Complications

Possible complications are as follows:

- Wound infections
- Pneumothorax
- Allergies
- Bar displacement
- Recurrence after bar removal.

b. **Surgical therapy for Pectus carinatum**

Generally patients with pectus carinatum are managed conservatively. Surgery is an option for symptomatic patients with dyspnea, pain or psychological distress [9]. The surgical repair in patients with pectus carinatum is classically the open Ravitch procedure (Fig. 4). The minimally invasive technique for the repair of pectus carinatum was described by Abramson [10].

This technique consists in a modified Nuss procedure, in which the pectus bar is inserted subcutaneously on top of the sternum and stabilized with wires on the ribs on both sides of the chest wall. This surgical technique is safe and feasible, but it has an higher rate of recurrence after bar removal [11].

2. Traumas

Traumatic sternal fracture or flail chest are relatively frequent and have a high morbidity and mortality. A flail chest is defined when two or more ribs are fractured in two positions on each rib, which causes a paxadoxical movement of the flail segment and therefore ineffective breathing. These fractures always cause strong pain, which, if not treated adequately, can lead to ineffective coughing, sputum retention and pneumonia. Displaced fractures can injure the lung and the intercostal vessels, leading to pneumothorax and hemothorax [12].

Classically, chest wall fractures are managed conservatively, however recent studies showed that an early surgical intervention in complex chest wall injuries can improve the patients' outcome [13]. Early stabilization reduces ICU and hospital stay, preserves the lung function and reduces the pain.

The common indications for rib and/or sternum stabilization are as follows:

- Ineffective breathing and mechanical ventilation,
- Chest wall deformity,
- Severe pain,
- Rib malunion.

Usually, titanium locking plated are used (for example the MatrixRIB system® and Synthes sternal fixation system®) to fix the rib and the sternum. Titanium is a very stable material, which has a low rate of allergic reactions [14].

Rib Stabilization

The patient is positioned supine, lateral or semi-lateral depending on the position of the rib fracture. After skin incision, the ribs are exposed preserving the muscles, if possible. It is always better to achieve a good stabilization rather than trying to keep the incision small and take the risk of bar dislodgement. The malunion or the sharp fragments of bones are removed and the ribs are re-approximated. It is particularly important to restore the natural shape of the chest and, in case of flail chest, to "pull up" the rib edges.

Then the rib thickness is measured and the appropriate screw is selected adding 2 mm. There are two different type of plates: the first are precontoured like each rib, the second are the eight-hole universal plates which can be bent adapting to the fractured rib. The fitting rib plate is selected and modeled to the rib contour. Then the plate is located on the fracture and at least three screws on each side are inserted, after creating the holes with a drill (Fig. 5). The screws will not hold in the long term on the costal cartilages, therefore it might be necessary to use a longer plate to reach the bony part of the ribs. We do not recommend to fix the plates with wires as they tend to reduce the blood supply to

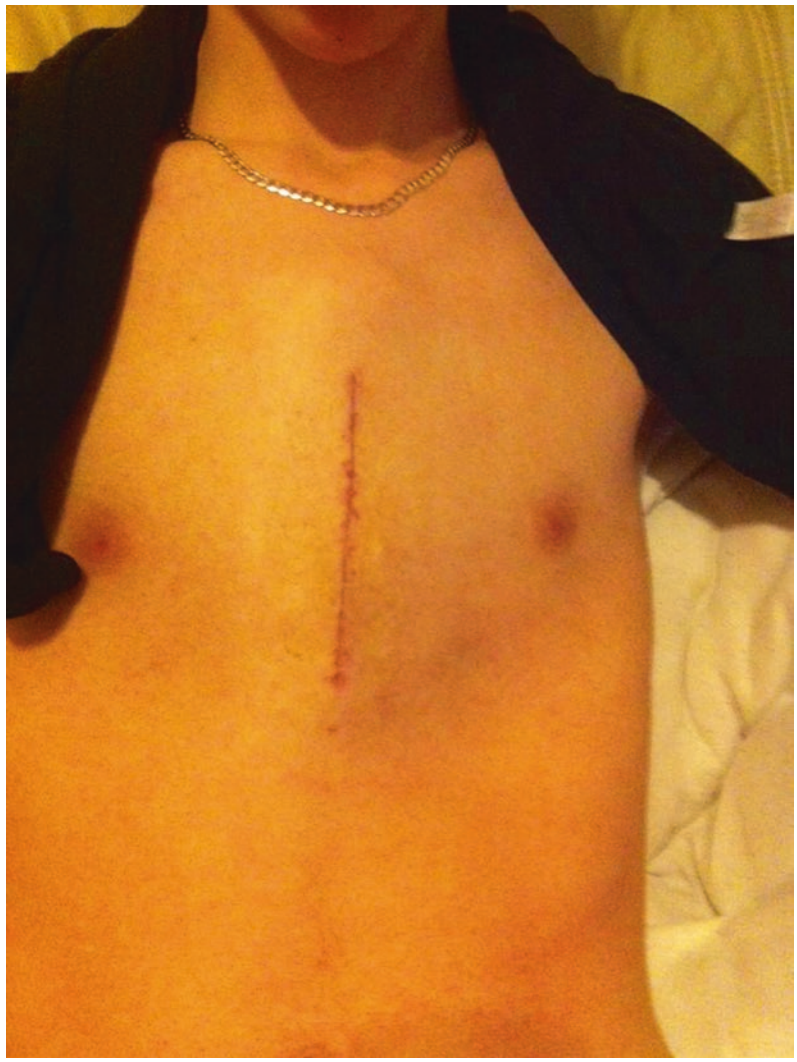

Fig. 4 Patient with perctus carinatum after surgery

the fracture. We recommend to get a CT marking to reduce the size of the incision.

Stabilization of sternal fractures

The patient is supine and the skin incision in vertical to expose the fractured sternum. Bone debris should be removed. In case of vertical fractures, a variety of sternal body or manubrium plates can be used, depending on the intraoperative situation. Sternal wires are rarely used in this kind of setting.

In case of transversal fractures, one or two plates are applied vertically with at least four holes on each side of the fracture. The thickness of the sternum is measured and the screws are chosen adding 3 mm. Then the appropriate plate is selected, bent and applied.

Fig. 5 Rib fixation with titanium plates

Complications

Complications after this kind of procedures are uncommon and include bleeding, infections, seromas, plate displacement.

Neoplastic Disease

Chest wall tumors include a variety of different entities and the patients' management changes according to the primary disease [15]. Chest wall neoplastic pathologies can be divided in 3 groups:

1. Primary chest wall tumors, benign and malignant (Table 1),
2. Chest wall metastases are rare and surgical resection is hardly ever indicated, generally in case of ulcerating tumors. Generally palliative radiation is the selected treatment method,

Table 1 Benign and malignant primary chest wall tumors

Benign	Malignant
Osteochondroma	• Skeletal
Fibrous dysplasia	Chondrosarcoma
Langerhans-cell histiocytosis	Osteosarcoma
Giant cell tumor	Ewing sarcoma
Aneurysmal bon cyst	Plasmacytoma
Lipoma	• Soft tissue
Desmoid tumor	Malignant fibrous histiocytoma
Neurogenic tumor	Liposarcoma
Fibroma	Angiosarcoma
	Rhabdomyosarcoma

3. Chest wall invasion from lung cancer
   Chest wall resection can be indicated in a multimodal therapy concept. Generally, in these cases, an en-bloc resection of the lung

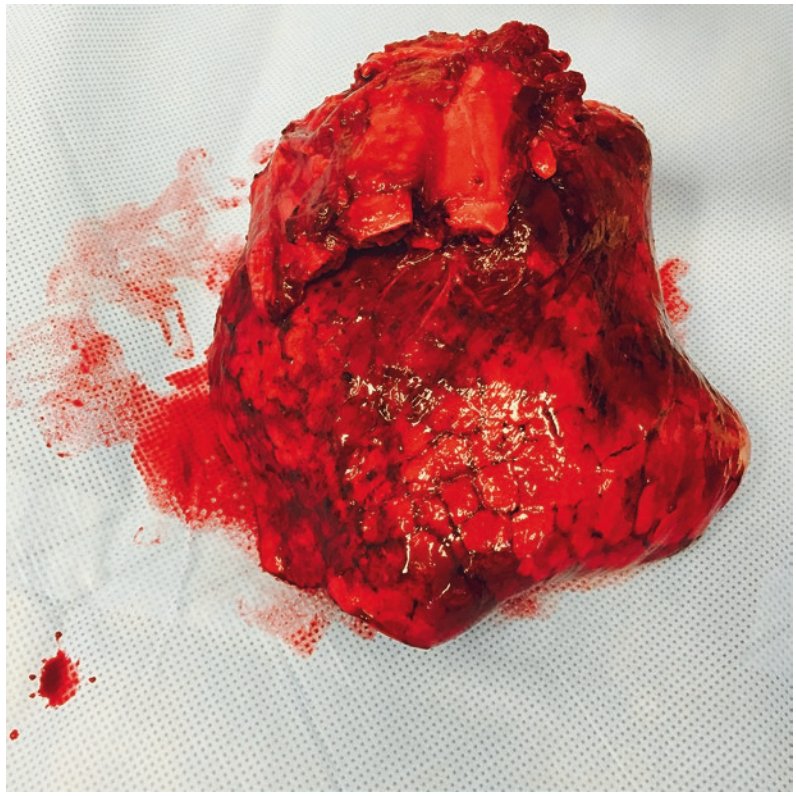

Fig. 6 Resection of the right upper lobe with 4 ribs

tumor and the infiltrated chest wall is performed, when the tumor stadium allows a curative resection (Fig. 6).

Preoperatively patient should be evaluated from different aspects. Together with the functional evaluation, the instrumental evaluation of the patients should be performed. A CT-scan of the chest should be performed in every patient and also a PET-CT in case of malignant diseases, to preoperatively evaluate the tumor extent. In many cases a biopsy is necessary to plan the right treatment strategy. For example, patients with a primary Ewing sarcoma of the chest wall should be treated in a multimodal setting with chemotherapy prior the surgical resection.

Once the indication for surgical resection is given, the surgical process consists in three different phases: tumor resection, reconstruction/stabilization and coverage of the soft tissue.

Tumor Resection

Resection of benign tumors should aim to the complete tumor resection without removing the muscles or the skin of the affected area.

Resection of malignant primary chest wall tumors consists normally in an en-bloc resection of the tumor and the surrounding tissues. The extent of the free resected margins is still debated, but it is generally acknowledged that the most important element to avoid relapse is the complete tumor resection (R0). Traditionally, one rib above and below the tumor should be removed, but new studies showed that a tumor free margin of 1 cm could be enough [16–18].

The same applies for the chest wall invasion by lung cancer [19].

The surgical resection of chest wall tumors should always be en-bloc with the surrounding tissue: muscles, skin and lung, if needed. In case

of invasion of the vertebrae, the operation should be performed together with the neurosurgeons. If a lobectomy must be performed, it should be done after the chest wall resection, in order to have more space to operate.

Chest wall reconstruction and stabilization

Chest wall stabilization may be required after the tumor resection and it depends on the size and the position of the defect. In fact, both length and number of resected ribs, as well as the defect location must be considered. If the defect is located in the anterior or lateral region of the chest, then a reconstruction is required. Defect located posteriorly or apically rarely cause chest wall instability, this happens only in case of large chest wall resections where the latissimus dorsi or the trapezius muscle must be resected.

There are many options and many materials available nowadays for the chest wall reconstruction. In many cases, the combination of two or more of following materials are used in the reconstruction.

a. Non-absorbable sutures
Non-absorbable intercostal sutures can be used to close the chest in case that only a single rib is resected. This method can be also used in combination with meshes or patches, which can be applied underneath the remaining ribs to give more stability.

b. Biocompatible Patches
On the market there are many kind of biocompatible meshes, synthetic or biologic. There are synthetic bioabsorbable meshes (e.g. GORE BIO-A Tissue Reinforcement®), which are replaced in circa 6 months with fibrotic scar tissue. Biological meshes can be made of acellular bovine pericardium (Veritas®) or of acellural porcine collagen (Permacol®). Both these meshes were originally designed for hernia repair or abdominal surgery, but their role is gaining importance also in the chest wall reconstruction. Bio-patches have a lower rate of postoperative infections, seromas and can be very useful alone or in combination with other reconstruction techniques with good long-time results [20–22) (Fig. 7).

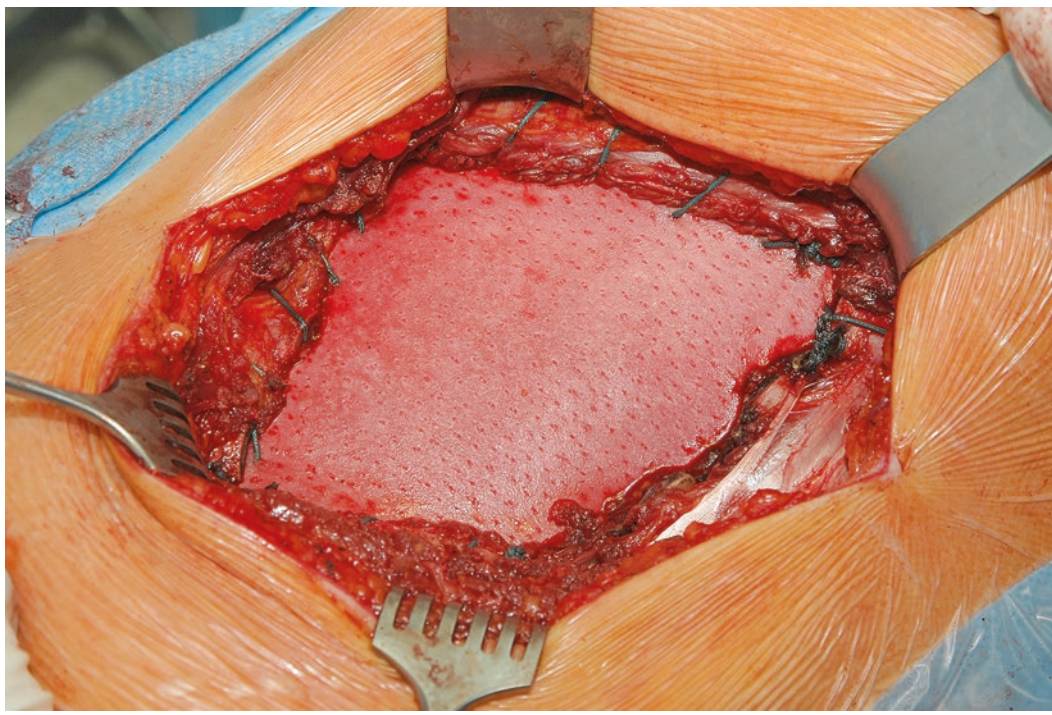

Fig. 7 Chest wall reconstruction with Permacol ®

c. Non-absorbable Patches
Nonabsorbable synthetic meshes are very frequently used in chest wall reconstruction. Their pore size is very important as the patch ability to integrate with the surrounding tissue depend on this factor. Meshes with micropores are for example polytetrafluoroethylene meshes (GoreTex®). They do not integrate very well with the surrounding tissue and induce therefore a reduced inflammatory response. They are impermeable and stay the same size long term.
Macropore meshes like polypropylene (Prolene®) have a good bio-integrability, are permeable and subject to shrinkage.
These meshes are generally fixed to the chest wall defect radially under tension with non-absorbable heavy sutures.

d. Bone grafts
Bone grafts are rarely used in chest wall reconstruction, more commonly following sternal resections. The graft can be autograft, allograft or xenograft. Allografts from a bone bank are most commonly used and they are previously processed to lose antigenic power. Their use is still experimental and there are only small series described in the literature. Intraoperatively the bone graft is shaped to match with the defect, than fixed with bars and screws.

e. The "sandwich technique" with methyl methacrylate
The "sandwich technique" was firstly reported in the 80s and it consists is two layers of polypropylene mesh containing methyl methacrylate acting as cement. The cement is good shapeable, but it is associated with a higher rate of infections [23].

f. Titanium plates
Titanium plates are commonly used for the reconstruction of large chest wall defect, as they are biocompatible and resistant [24]. They are oft used in combination with meshes and offer an excellent stability.

Soft tissue coverage

The last step of chest wall reconstruction is the coverage of the selected prosthetic material with soft tissues. A multidisciplinary collaboration with the plastic surgeons may be needed in selected cases. Usually, the soft tissue coverage is provided by muscular flaps. The flap vascularization has to be preserved during the surgery to have successful results.

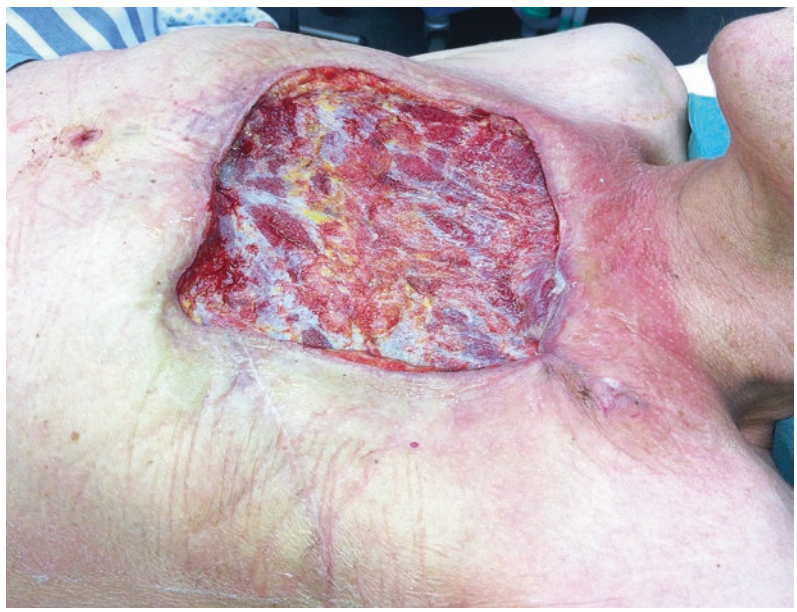

Fig. 8 Soft tissue coverage with Latissimus dorsi muscle

Different muscles can be used as flap:

- *Pectoralis major muscle*, mostly used in sternal reconstructions;
- *Latissimus dorsi muscle*, most common muscle flap for reconstructing the chest wall (Fig. 8);
- *Serratus anterior muscle* for intrathoracic employement;
- *Rectus abdomini muscle* for anterior defects;
- *Omentum*, alternative in particular cases like wound infections.

Conclusions

Chest wall surgery is challenging as it includes many varieties of diseases and, therefore, treatment options. In this field there is a constant evolution of the surgical techniques and materials, which require a particular passion and expertise.

Self-study

1. Which are the possible complication after Nuss procedure for pectus excavatum? (You can choose more than one answer)
   (a) Bar displacement
   (b) Recurrence after bar removal
   (c) Neoplastic degeneration
   (d) Pneumothorax.
2. Which are the common indications for rib and/or sternum stabilization after chest trauma?
   (a) Ineffective breathing and mechanical ventilation
   (b) Chest wall deformity, severe pain and rib malunion
   (c) All of the above
   (d) None of the above.
3. Which of the following statement is true?
   (a) Chest wall reconstruction should be always performed after chest wall resection for neoplastic disease
   (b) Chest wall reconstruction should be performed if the defect is located in the anterior or lateral region of the chest after chest wall resection for neoplastic disease
   (c) Chest wall reconstruction should be performed if the defect is located posteriorly or apically in the chest after chest wall resection for neoplastic disease
   (d) Chest wall reconstruction should never be performed after chest wall resection for neoplastic disease.

Answers

1. Which are the possible complication after Nuss procedure for pectus excavatum? (You can choose more than one answer)
   (a) Bar displacement - **CORRECT**
   (b) Recurrence after bar removal - **CORRECT**
   (c) Neoplastic degeneration
   (d) Pneumothorax—**CORRECT**.
2. Which are the common indications for rib and/or sternum stabilization after chest trauma?
   (a) Ineffective breathing and mechanical ventilation
   (b) Chest wall deformity, Severe pain and rib malunion
   (c) All of the above—**CORRECT**.
   (d) None of the above.
3. Which of the following statement is true?
   (a) Chest wall reconstruction should be always performed after chest wall resection for neoplastic disease
   (b) Chest wall reconstruction should be performed if the defect is located in the anterior or lateral region of the chest after chest wall resection for neoplastic disease—**CORRECT**.
   (c) Chest wall reconstruction should be performed if the defect is located posteriorly or apically in the chest after chest wall resection for neoplastic disease
   (d) Chest wall reconstruction should never be performed after chest wall resection for neoplastic disease.

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Surgical Anatomy of the Trachea and the Central Bronchial Airways

Patrick Dorn and Gregor J. Kocher

Key Points

1. Knowledge of the anatomy of the trachea and the central bronchial airways, as well as the relations between its adjacent structures and understanding of pathophysiologic influences of different pathologic conditions are of vital importance for the surgeon in order to allow for an adequate evaluation of the treatment, operability, and technique of resection.
2. Tumors of the trachea or the central bronchial system are rare and primary tracheal tumors are potentially curable by resection.
3. The most frequent etiology of non-neoplastic tracheal stenosis is the post-intubation stenosis. Far less frequent are post-traumatic, congenital, inflammatory/infectious stenosis or stenosis due to extrinsic compression, e.g. goiter or acquired vascular lesions.
4. Anesthetist and surgeon have to be a well-established team to offer the patient a maximum of safety during surgery.
5. Reconstruction of the airway can be performed in different ways according to the extension of the resection and according to the experience of the surgeon with the aim of obtaining a tension-free anastomosis, which subsequently reduces the possible the risk of post-operative complications due to healing problems.

The trachea acts not only as anatomical part for the ventilation, but also plays an important role in clearing of tracheal and bronchial secretions.

Knowledge of the anatomy of the trachea and the central bronchial airways, as well as the relations between its adjacent structures and understanding of pathophysiologic influences of different pathologic conditions are of vital importance for the surgeon in order to allow for an adequate evaluation of the treatment, operability, and technique of resection. The trachea is composed of a cartilaginous (ventrolateral) and a membranous part (posterior). Its shape and dimension depend on age, sex and body size. In an adult person, the length is between 10 and 13 cm, the coronal diameter approximately 2–2.5 cm, the sagittal diameter ranges from 1.4 to 1.8 cm, and the wall thickness is about 3 mm. The shape changes from a circular (1. Year of life) to a U- or C-shaped trachea in its cross-section. The trachea consists of 18–22 cartilage rings, which can also be used as parameter to estimate the intraoperative length: two rings measures up to 1 cm. The tracheal lumen narrows slightly as it progresses towards the bifurcation, which normally lies in projection at the level of the sternal angle anteriorly and the fourth or fifth thoracic vertebra posteriorly (Picture 1). The carina is formed by the right main bronchus which goes off at an

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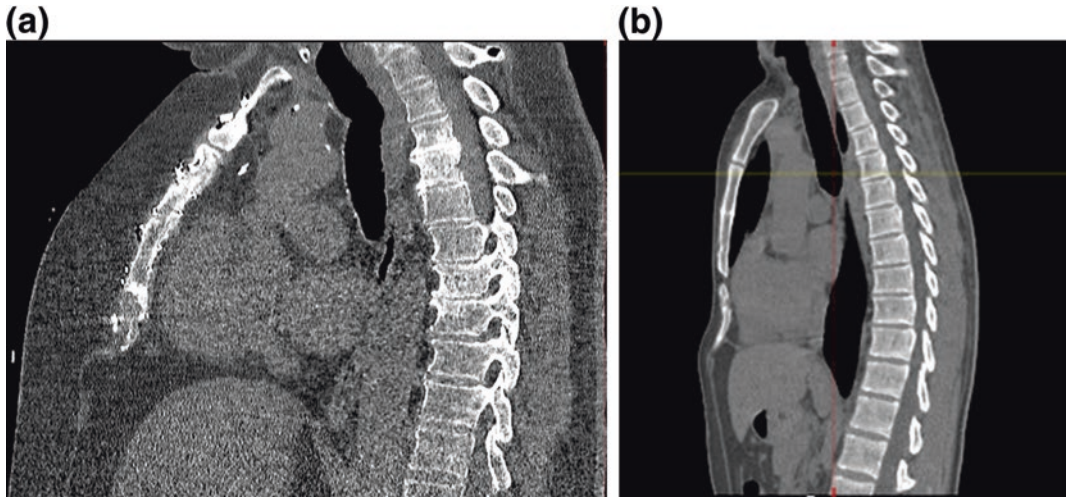


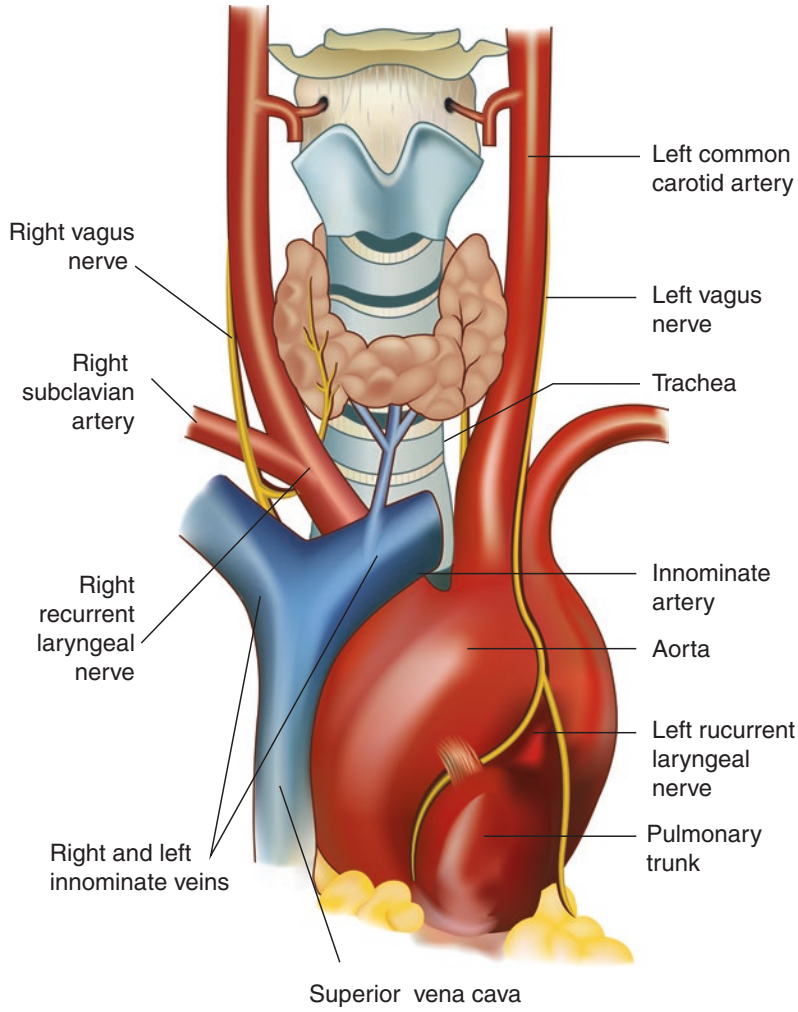
Picture 1 Sagittal projection through trachea/carina of a 72 (**a**) and 30 years old man (**b**)

angle of about 30° to the trachea and by the left main bronchus, which originates with an angle between 55 and 75° [1].

The central location of the trachea, very important surrounding structures and its bradytrophic tissue are some anatomical challenges, which the thoracic surgeon has to face with (Pictures 2 and 3). The knowledge of the frequent irregularity of its blood supply is another central point. Despite a wide variability, in general the cervical part of the trachea is supplied by 3 branches of the inferior thyroid artery, which originate from the subclavian arteries and which pass either anteriorly or posteriorly to the recurrent laryngeal nerves. The second and third branches additionally supply the esophagus. The artery branches form a rich network of anastomoses with the arterial branches from below [2]. The blood supply of the lower trachea and the carina is usually provided by three bronchial arteries, which arise from the descending aorta. One anterior branch of the superior bronchial artery goes to the proximal left main bronchus and the anterior aspect of the carina, and its posterior branches pass the esophagus posteriorly towards the right main bronchus. Despite a great variation in bronchial arterial anatomy, the right main bronchus is often additionally supplied by one right-sided aortic branch and the left main bronchus is supplied by two left-sided aortic branches.

The blood supplying arteries enter the lateral walls of the trachea in a segmental fashion from posterolateral direction throughout its length (Picture 4). About 0.7–1.5 cm anteriorly to the trachea-oesophageal groove, the branches of the arterioles run into an anastomotic submucosal plexus. To prevent complications, the blood supply and the nutritive layer of the trachea and the central bronchi should be preserved, so that not more than 1–2 cm of trachea should be dissected above and below the anastomosis.

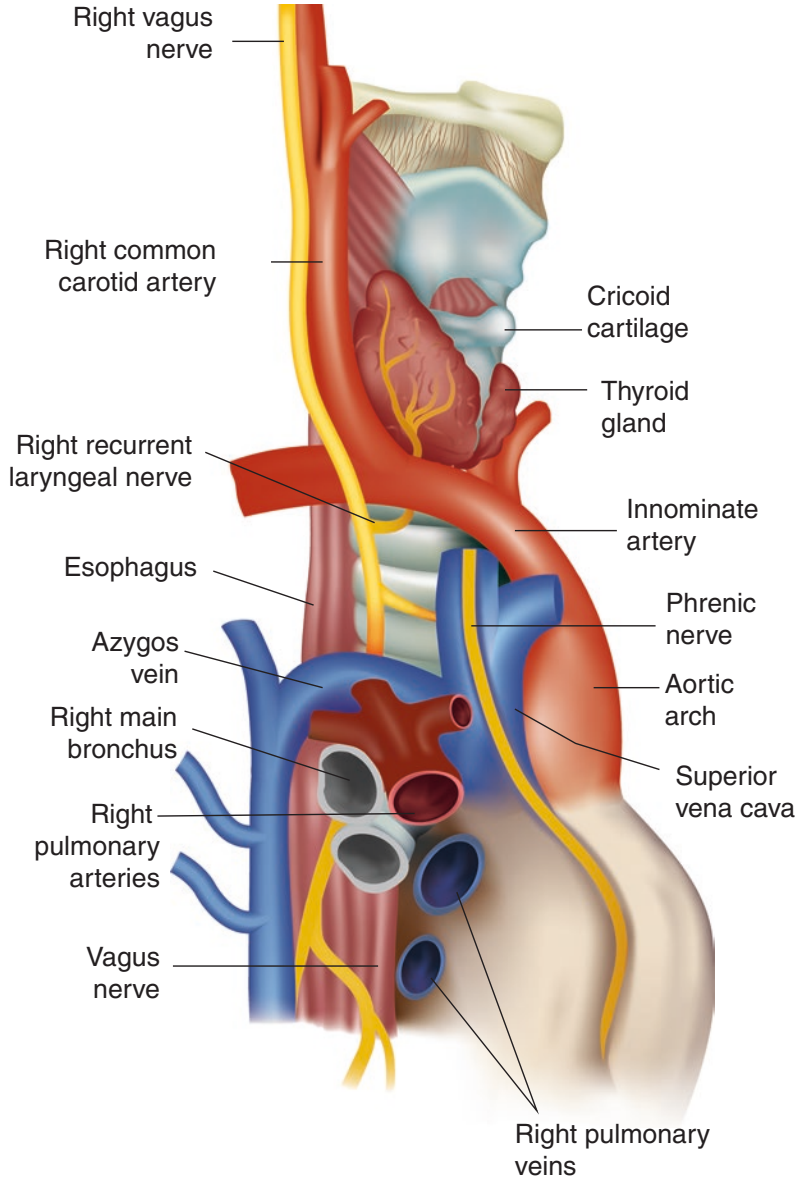
Intraluminally, the trachea is covered with respiratory mucosa consisting of ciliated pseudostratified columnar epithelium, which is able to move debris towards the larynx by rhythmic contraction of the cilia at a rate of 160–1500 contractions per minute and with a speed of 16 mm per min [1, 3]. After debris is wafted by



Picture 2 Neighbouring structures of the trachea (front view)

this ciliary action proximally from more distal airways, the mucoid material is then either expectorated or swallowed. Mucous glands are present in the submucosa and are connected to the surface by ducts. Irritative substances to the mucosa, e.g. tobacco smoke, may produce squamous metaplasia and damage to the cilia. Patients need an adequate cough to clear their respiratory secretions in this condition. The total volume of tracheobronchial secretions varies normally from 10 mL/d to 100 mL/d, depending on regulation by vagal and parasympathetic stimulation and goblet cells under the influence of local irritants.

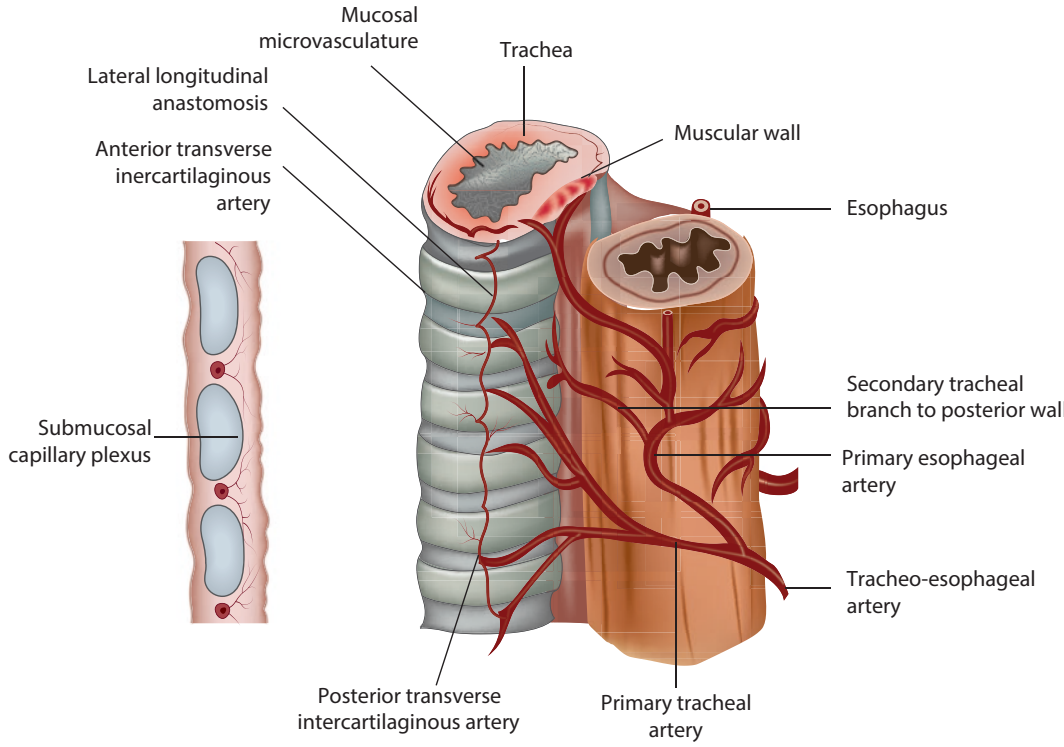
Congenital variants or anomalies of the tracheobronchial system are seen in 1–12% of patients after bronchography or bronchoscopy [4], which may be important for surgical planning. Developmental interruption can be classified as:



Picture 3 Neighbouring structures of the trachea (view from right side)

- Agenesis (absence of bronchi, vessels and lung parenchyma; tracheal agenesis is not compatible with life)
- Aplasia (absence of lung parenchyma with blind rudimentary bronchi present; tracheal aplasia is not compatible with life)
- Hypoplasia (decrease in the number and size of bronchi, vessels and parenchymal structures).

Furthermore, an understanding of the pathophysiologic complications of factors such as chemotherapy, radiation and steroid therapy



Picture 4 Trachea's blood supply

helps the surgeon to recognize the limitations of surgical procedures and avoid complications.

Self-study

1. Which bronchus arises in projection above the level of the pulmonary artery ('eparterial bronchus')
   (a) Bronchus principalis sinister
   (b) Bronchus lobaris superior sinister
   (c) Bronchus lobaris superior dexter
   (d) Bronchus lobaris inferior dexter
2. Which vertebral level does the carina of the trachea usually project to?
   (a) Vertebra thoracis 1
   (b) Vertebra thoracis 3
   (c) Vertebra thoracis 5
   (d) Vertebra cervicalis 7.

Answers

1. (c)
2. (c)

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General Aspects in the Pathology of the Trachea

Patrick Dorn and Gregor J. Kocher

Key Points

1. Knowledge of the anatomy of the trachea and the central bronchial airways, as well as the relations between its adjacent structures and understanding of pathophysiologic influences of different pathologic conditions are of vital importance for the surgeon in order to allow for an adequate evaluation of the treatment, operability, and technique of resection.
2. Tumors of the trachea or the central bronchial system are rare and primary tracheal tumors are potentially curable by resection.
3. The most frequent etiology of non-neoplastic tracheal stenosis is the post-intubation stenosis. Far less frequent are post-traumatic, congenital, inflammatory/infectious stenosis or stenosis due to extrinsic compression, e.g. goiter or acquired vascular lesions.
4. Anesthetist and surgeon have to be a well-established team to offer the patient a maximum of safety during surgery.
5. Reconstruction of the airway can be performed in different ways according to the extension of the resection and according to the experience of the surgeon with the aim of obtaining a tension-free anastomosis, which subsequently reduces the possible the risk of post-operative complications due to healing problems.

Tumors of the trachea or the central bronchial system are rare. More common, tracheal obstructions are seen because of an invasion by metastatic lymphnodes or primary tumors arising from adjacent organs. In adults, 90% of the tracheal tumors are malignant. Mostly, these tumors are localized in the distal trachea or close to the bifurcation. In many cases, they are central bronchial carcinomas which infiltrate the bifurcation, the tracheobronchial angle or distal trachea [1, 2]. Primary tracheal tumors are potentially curable by resection. An exception of other 'tracheal' tumors originating from surrounding structures, which can also potentially get completely removed in a curative intention by a tracheal resection are some thyroid carcinomas invading the trachea. The location of the tumor influences the technical aspects and risk of surgical therapy (Picture 1):

- Tumors involving the subglottic space
- Tumors involving the proper trachea
- Tumors involving the carinal proximity.

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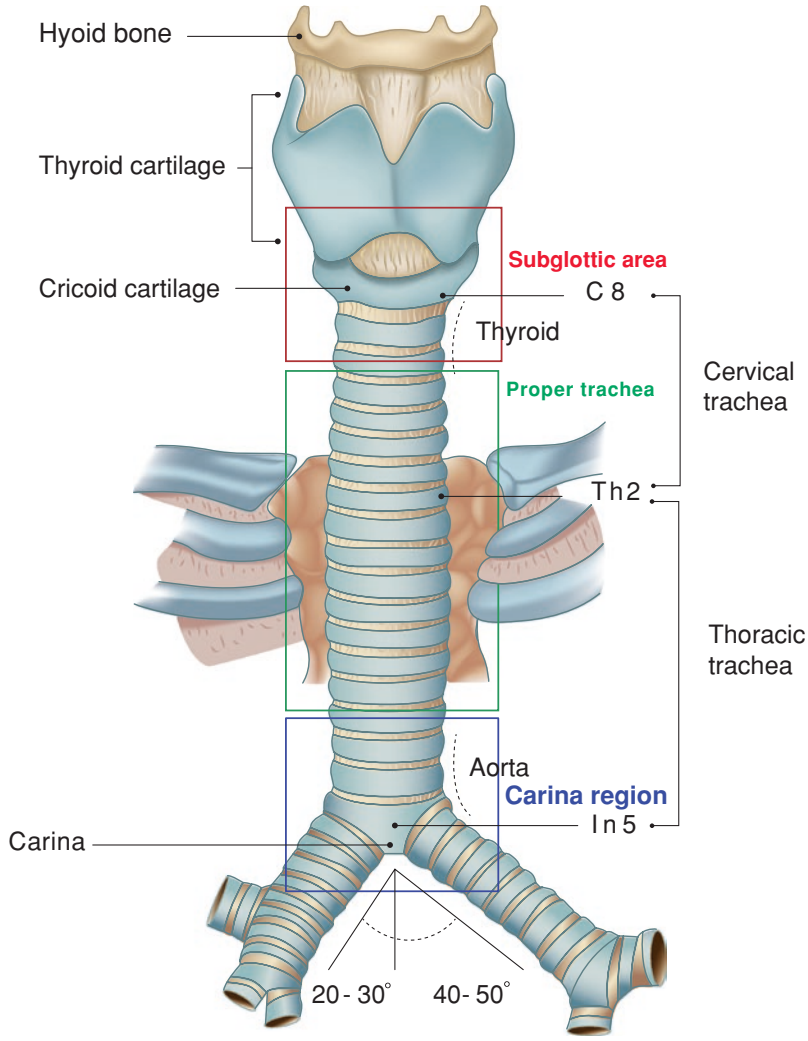
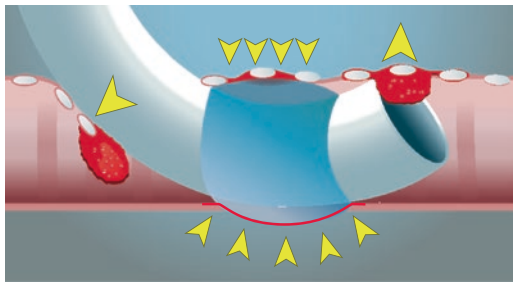


Picture 1 Anatomical division of the trachea

Histopathologically, adenoid cystic carcinoma and squamous cell carcinoma are the most frequent tracheal tumors, followed at great distance by carcinoids, sarcomas and mucoepidermoid carcinomas.

To mentioning as non tumor-caused indications for surgical interventions of the trachea are intubation associated complications, notably post-intubation stenosis or malacia.

Tracheal stenosis: The most frequent etiology of non-neoplastic tracheal stenosis is the post-intubation stenosis. Far less frequent are post-traumatic, congenital, inflammatory/infectious stenosis or stenosis due to extrinsic compression, e.g. goiter or acquired vascular lesions. Post-intubation stenosis result from cuff lesions induced by endotracheal or tracheotomy tubes or from the sequelae of tracheotomy (Picture 2). A stenosis after intubation became a rare problem thanks to technical evolution, but remains a serious challenge if it occurs. A long-lasting ischemia, for example because of a too high cuff pressure compared to the capillary pressure in the tracheal mucosa layer, can provoke ulcerations or chondropathia of the cartilage rings. An excessive fibrotic remodeling can lead to stenosis. Additional possible risk factors are the size of the airway tube in relation



Picture 2 Vulnerable zones for lesions from tracheotomy tube

to the diameter of the trachea, the cuff material, the time period of the intubation, cardiovascular problems from patients side, patients age, and medication with steroids [3].

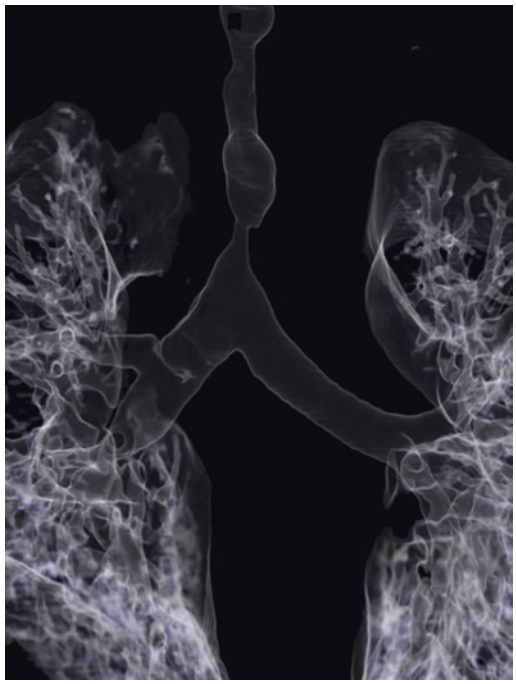
Tracheoesophageal fistula: The incidence of tracheoesophageal fistula after long-term intubation had decreased over time. This positive development is mainly due to the evolution of low pressure and large volume cuffs. Because of its potential consequences, as for example aspiration pneumonia or prolonged compulsory ventilation support, there is a major relevance regarding health economy [4, 5]. Pathophysiologically, the cuff provokes a pressure-caused erosion mostly at the membranous part of the trachea and the directly adjacent esophagus. Sometimes this damage is additionally worsened by a gastric tube or the spine serving as counter bearings. Organic airway stenosis has to be suspected in all patients with obstructive symptoms and previous intubation.

In infants, tracheal stenosis is most commonly related to congenital anomalies. The two most frequent pathologies of the intrathoracic airways are tracheomalacia and tracheal stenosis. In toddlers and even in adults, tracheomalacia is characterized by reduced rigidity of the tracheal wall, which was caused by structural changes of the tissue. Whereas in adults it is provoked secondarily, for example after long-term intubation or in chronic obstructive pulmonary disease (COPD), it is a primary malformation during organ development in infants. Potential etiologies can be subdivided in intrinsic (reduced content of cartilage and increased proportion of pars membranacea) and extrinsic defects (rare; for example because of special anatomical features, e.g. extrinsic compression from cardiovascular malformations). Even after correcting the anatomical anomaly, localized tracheomalacia may necessitate further specific trachealsurgery surgery. Noticeable is how often congenital tracheomalacia is associated with esophageal atresia and tracheoesophageal fistula. It has also been described as complication after surgicaltreatment for the latter [6].

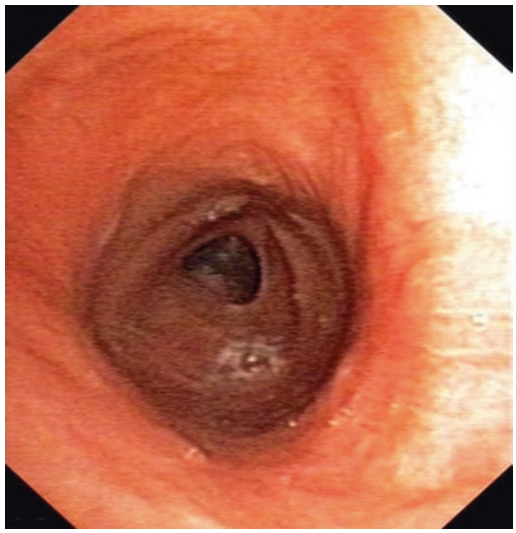
The true incidence of tracheomalacia in adults is difficult to estimate; it is expected to be up to 23% in high-risk population, as e.g. in patients with COPD. A possible explanation of the higher frequency in men could be the higher rate of smoking. Histologically and pathophysiologically, it is characterized by softening of tracheal structure, flaccidity of anterior cartilaginous wall, widening of the posterior wall and consequent tracheal obstruction during expiration. Affection of both structures, trachea and bronchial system (tracheobronchomalacia) is more frequent than only one of them (tracheomalacia > bronchomalacia).

Symptomology and Diagnostics

Symptoms caused by tumors of the trachea and the central bronchi are non-specific. Patients are sometimes complaining about chronic cough and an increasing exercise intolerance. Tumors close to the carina with consecutive stenosis of one main bronchus can provoke a wheezing and humming on the equilateral lung, described as ‘unilateral asthma’ [7]. Stridor and hemoptysis are normally clinical signs of extended disease. Reduced inspiratory flow and severe obstruction are potential signs of an extra thoracic stenosis at the central airways in the lung function analysis. Chest X-ray is mostly inconspicuous or showing a total atelectasis of the affected lung. CT scan of the chest gives information about intra- and extra-luminal tumor extension and its location in relation to neighbouring organs and vessels (Picture 3). The best examination so far for evaluation of these tumors is the rigid or flexible bronchoscopy (Picture 4). It allows



Picture 3 Two-level-stenosis after long-term intubation (CT scan reconstruction and endoscopic situation)



Picture 4 Two-level-stenosis after long-term intubation (CT scan reconstruction and endoscopic situation)

measuring of the tumor extension in relation to the vocal cords and the carina. The grade of obstruction can be evaluated dynamically with the additional option of a partial tumor resection as bridging procedure before definitive surgical or non-surgical intervention is planned or for tumor biopsy for histologically confirmation of the diagnosis. An endoscopic examination under jet-ventilation and apnea enhances the informative value. Thus, acutely life-threatening complications due to the obstruction, the swelling of the tumor after manipulation, or due to bleedings are more manageable.

The onset and character of symptoms due to a stenosis depends on its dimension. Severe respiratory distress, feeding problems, inability to expectorate and recurrent pneumonia are possible symptoms of a significant stenosis. A bronchoscopy is helpful to confirm diagnosis. A CT scan is needed to specify the stenosis and to evaluate potential structure anomalies. Mostly, the occurrence of symptoms is one to six weeks delayed after removal of the airway tube [8, 9]. A possible explanation for this is that a progression of the stenosing scar to over 50% of the lumen is necessary to provoke clinical changes. Only exertional dyspnea may occur as an unspecific and mild clinical sign, if the residual lumen has a diameter larger than 5–6 mm. A bronchoscopy and CT scan is usually performed as further diagnostics.

As shown in a study of Gaissert et al. [10], the mean interval between the onset of symptoms and diagnosis is 12 months for malignant tracheal tumours, mainly depending on anatomical and clinical pattern, and also on speed of tumour growth. This is an important fact with regard to curative treatment, because resectability diminishes with diagnostic delay.

Recurrent cough after swallowing is the leading symptom of a tracheoesophageal fistula in non-intubated patients, whereas an increased production of sputum and concomitant problems to seal the cuff are indicators for this complication in intubated patients. An increased risk of pneumonia or reflux disease because of consecutive abdominal distension after ongoing swallowing of air with worsening of the respiratory situation are possible consequences. The fistula is located in the subglottic region between the second and the fifths tracheal ring in intubated

patients or distally adjacent to the tracheostoma in patients with a tracheotomy. The best diagnostic is done by bronchoscopy, occasionally completed with a radiological representation of the fistula with contrast agent.

A low grade tracheomalacia is commonly asymptomatic. Expiratory wheezing or stridor, potentially accompanied with a barking cough or problems to mobilize sputum can be seen in serious luminal restriction. A dynamic visualization by bronchoscopy belongs to the diagnostic standard in tracheomalacia. A dynamic CT scan can lead to additional information.

Patient Selection and Workup

Preoperative evaluation for all patients includes clinical history, physical examination, routine blood tests, pulmonary and cardiac function test such as spirometry, arterial blood gas analysis, perfusion lung scan and electrocardiography. Total body computed tomography (CT) and, in case of malignancy (e.g. NSCLC or primitive airway tumors), a positron emission tomography with fluorodeoxyglucose (PET) are routinely performed to evaluate the lesion and the infiltration of the surrounding structures as well as to ensure the absence of a metastatic disease. Bronchoscopy is the most important preoperative tool to identify the lesion and to plan the surgical resection. In fact. The diagnosis of the lesion is usually obtained by endobronchial biopsy or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) which also allows to evaluate the extension of the tumor, to identify suspicious paratracheal tumor spreading and to assess mediastinal nodal involvement in case of suspicious of N2 disease on CT or PET scan. In case of histologically proven N2 disease, the patients should be candidates to induction chemotherapy and then re-staged with a total body CT and PET scan to schedule the responders or the patients with stable disease for surgery. Endobronchial biopsies are important in order to map the trachea and to detect the limits of surgical resection avoiding intraoperative surprises and extensive tension on the anastomosis afterwards. Cervical mediastinoscopy should be performed in order to confirm a suspected infiltration of the tracheobronchial angle and to better plan the extension of the resection. During a multidisciplinary meeting, thoracic surgeons and oncologists confirm patients' resectability and the induction treatment plans, if needed.

In case of NSCLC with carinal involvement, induction chemotherapy is indicated with the aim of downstaging the tumor, increasing the resectability and reducing the extension of the resection other than improving long-term survival by controlling potential systemic micrometastasis. Furthermore, the patient has usually a better compliance to induction therapy rather than adjuvant therapy; patient's performance status and clinical condition are usually better than after an extended surgery when post-operativecomplications complications could delay the beginning of any adjuvant treatment. On the other hand, theoretical disadvantages of induction chemotherapy are a possible progression of the disease during the treatment, possibly rendering a patient inoperable, more surgical difficulties and a possible increase of post-operative morbidity and mortality. Contraindications for tracheal resection are impaired respiratory or cardiac function, extension of the tumor that hamper a tension free anastomosis, multiple N2 or N3 lymphnode stations involvement and presence of distant metastasis. Preoperative irradiation more than 45 Gy is not an absolute contraindication to tracheal resection, but it should be avoided because of consecutive impaired blood supply and increased risk of anastomosis insufficiency.

Challenges for Anesthesia

Sufficient oxygenation of the patient is one of the main cornerstones, especially when operating on the more central airways such as the carina and/or trachea. To perform central airway resections and reconstructions, there are basically two options in order to maintain lung ventilation: an intra-surgical field tracheal tube

or ventilation by high frequency jet ventilation (HFJV) [11–13]. In the first option, a sterile circuit is passed through the operative field and prepared to directly ventilate one single lung. Despite of central airway surgery being usually more complex and time-consuming procedures, the additional cross-field ventilation is a successful option in different central trachea- and carinoplasties, and is therefore used in the vast majority of cases [14, 15]. One of the disadvantages of this technique is, that the cross-field tube can sometimes obstruct the view of the reconstruction site, thus periodical retraction of the tube may sometimes be necessary when performing airway anastomosis in order to improve exposure [16]. In case of HFJV, the catheter can be easily introduced through the endotracheal tube and thanks to its small diameter obstruction of the view of the anastomotic site is far less problematic. Furthermore, no additional manipulations including the possible need for an additional incision for introduction of the cross-field ventilation tube are needed [17–21]. However, moderate ventilation of the lung on the operative site may be observed which may affect optimal exposure, especially when using a minimally invasive approach. Additionally, there is a certain risk of barotrauma, which in rare cases can result in an acute respiratory distress syndrome (ARDS) [16, 22, 23].

Extracorporeal membrane oxygenation (ECMO) has also been reported with good results in case of impossibility of endotracheal intubation such as severe tracheal stenosis or complete obstruction [24, 25]. In these cases a single lumen veno-venous ECMO may nowadays be used to facilitate airway surgery thanks to a tubeless operation field, which in the end may possibly allow for a more accurate resection and reconstruction as well as a more definitive airway security.

The experience of the anesthetist in the field of these special ventilation techniques as such is therefore very relevant and a prognostic factor for the outcome of the operation. Anesthetist and surgeon have to be a well-established team. This is the only way to offer the patient a maximum of safety during surgery.

Self-study

1. What is the leading symptom in non-intubated patients with tracheoesophageal fistula?
   (a) Wheezing
   (b) Inspiratory stridor
   (c) Coughing after swallowing
   (d) Burping
2. From onset of symptoms to diagnosis: Which tumor has the largest interval?
   (a) Tracheal sarcoma
   (b) Tracheal carcinoid
   (c) Unresectable adenoid cystic carcinoma
   (d) Resectable adenoid cystic carcinoma.

Answers

1. c
2. c

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Surgical Approaches

Patrick Dorn and Gregor J. Kocher

Key Points

1. Knowledge of the anatomy of the trachea and the central bronchial airways, as well as the relations between its adjacent structures and understanding of pathophysiologic influences of different pathologic conditions are of vital importance for the surgeon in order to allow for an adequate evaluation of the treatment, operability, and technique of resection.
2. Tumors of the trachea or the central bronchial system are rare and primary tracheal tumors are potentially curable by resection.
3. The most frequent etiology of non-neoplastic tracheal stenosis is the post-intubation stenosis. Far less frequent are post-traumatic, congenital, inflammatory/infectious stenosis or stenosis due to extrinsic compression, e.g. goiter or acquired vascular lesions.
4. Anesthetist and surgeon have to be a well-established team to offer the patient a maximum of safety during surgery.
5. Reconstruction of the airway can be performed in different ways according to the extension of the resection and according to the experience of the surgeon with the aim of obtaining a tension-free anastomosis, which subsequently reduces the possible the risk of post-operative complications due to healing problems.

Reconstruction of the airway can be performed in different ways according to the extension of the resection and according to the experience of the surgeon with the aim of obtaining a tension-free anastomosis which subsequently reduces the possible the risk of post-operative complications due to healing problems of the suture. For the indication of the surgical treatment and the prevention of complications, the knowledge of risk factors for tracheobronchial resection and reconstruction is essential: Systemic steroid therapy, neoadjuvant radiotherapy (>50 Gy), anastomosis with tension, or tracheobronchial instability [1, 2]. In addition, the expansion of the tumor in terms of length as well as the infiltration of mediastinal organs is very important when the decision for a tracheal resection has to be made. For simple tracheal stenosis, a segmental resection using an end-to-end anastomosis with immediate postoperative extubation, is the method of choice for treatment in adults and children. In the latter group, a slightly prolonged intubation may be necessary postoperatively. The important question is how much length of the trachea can be resected

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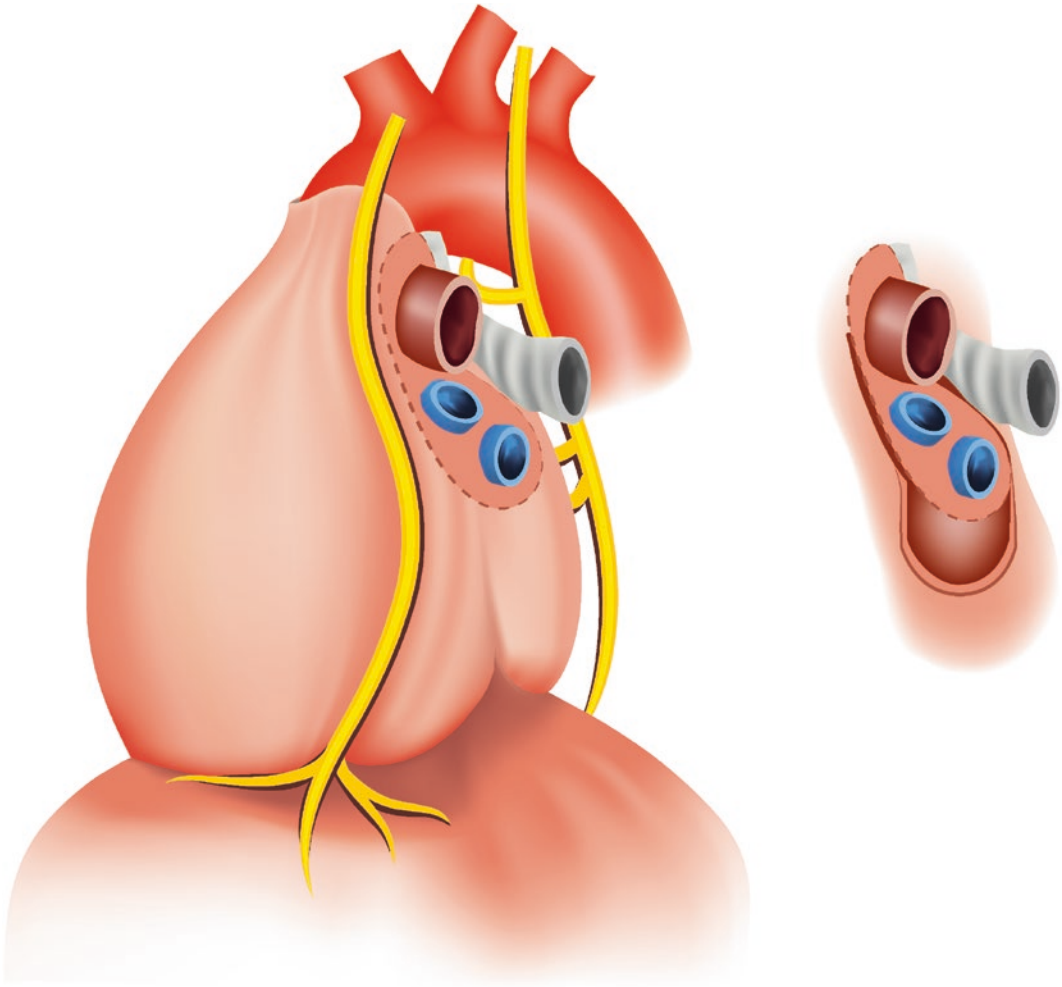
by at the same time allowing a tension free anastomosis. The resectable length depends on the patient's age, physique, height, and any prior surgery performed. Without any supplementary mobilization maneuvers, a resection of about 2–3 cm of the trachea is feasible. With extensive mobilization maneuvers, even up to two thirds of the trachea are resectable.

Carinal resection is defined as the resection of the tracheo-bronchial bifurcation with or without lung resection. Carinal resection and reconstruction without lung resection is very rare and is usually indicated in case of primary tumors of the carina or the distal trachea. More frequently, carinal resection is associated in case of lung resection for a non-small cell lung cancer (NSCLC) infiltrating the tracheo-bronchial bifurcation. For resection of the bifurcation an anastomosis between trachea and main bronchus is possible after resection of up to 4 cm [3–5]. Otherwise extended mobilization is necessary, possibly in addition to an extra-anatomical or anatomical parenchymal resection. For multilevel stenosis, a two-stage approach is sometimes necessary if the tracheal segment that needs to be resected is too long [6]. Infiltration of the esophageal mucosa or of the aorta are contraindications for primary resection. Lymph node metastases per se are not an exclusion criterion depending on histology and levels and numbers of infiltratedlymph nodes [7]. As a general rule, functional and oncological operability/resectability have to be fulfilled in any case. The location of the tumor influences the technical aspects and risks of surgical therapy (tumors involving the subglottic space, the proper trachea, and the carinal proximity).

Surgical approaches differ depending on localization of the tumor and extension of the resection:

- Cervical approach (possibly in combination with upper sternal split (i.e. manubriotomy)): access to the laryngo-tracheal region and proximal third of the trachea.
- Sternotomy, possibly with extension to an additional cervical approach: access to the middle third of the trachea and to the tracheobronchial bifurcation.
- Posterolateral thoracotomy (4th or 5th intercostal space) right side: access to the distal third of the trachea, bifurcation, left proximal main bronchus and right bronchial system.
- Posterolateral thoracotomy (4th or 5th intercostal space) left: access to bifurcation and left main bronchus.

A key prerequisite for avoiding complications is a tension-free anastomosis [1, 7]. The pretracheal fascia has to be incised and opened in any case to mobilize the trachea. In contrast to this anterior dissection, the lateral attachment of the trachea shouldn't be loosened extensively because of the blood supply, which enters laterally through the tracheal wall. There are different mobilization techniques depending on the part of the central airway planned to be resected: trachea, bifurcation or hilus of the lung:



Picture 1: Opening of the pericardium after dividing of the pulmonary ligament to mobilize the hilum

- Flexion of the head	2–4.5 cm
- Dividing of the pulmonary ligament and opening of the pericardium to mobilize vein to the upper and intermediate lobe (Picture 1)	2–3 cm
- Mobilization of the aortic arch and dividing of the Botalli ligament	0.5–1 cm
- Mobilizing of the bifurcation and distal trachea	0.5–1 cm
- Suprahyoidal mobilization of the larynx (Montgomery)	1–2.5 cm
- Pericardiophrenic mobilization (Macchiarini)	2–3 cm
- Extra-anatomical reimplantation of main bronchus	2–3 cm

General operative aspects

Denudation, skeletonizing and blunt preparation of the central airway may significantly harm its nutritive layer. Therefore, it is important to preserve the tracheal and bronchial fascia. This is the only way to maintain the rich network of vascular anastomoses and to avoid postoperative healing problems of the anastomosis. Additionally, using electrocautery is a risk factor for thermic damage of this vulnerable blood supply. In case of malignancy the lymph nodes of the upper and lower mediastinum have to be resected in form of a complete compartmental dissection. Whenever possible, the contralateral mediastinum should be also taken into account

and included in a complete resection. A preoperative mediastinoscopy should be avoided whenever possible because of the potential damage of the nutritional situation, as mentioned before.

Preparation of the patient is important. For tracheal resection through a collar incision, neck extension is achieved by inflating a thyroid bag under the shoulders. The patient is prepped from chin to xiphoid process in case sternotomy is required [8].

In case of operative treatment for tracheal tumor, the resection starts with sharp cutting of the intercartilaginous area distally after clear endoscopic definition of the resection margins. Placement of the cross-field tube into the distal trachea or bronchus and consecutive blocking of the cuff or fixation of the tube with a fixation knot. Subsequently, the division of the proximal margin is performed. Frozen section analysis is recommended to confirm R0-resection. A R1-resection can only be tolerated if there is no safe option for further resection and the tumor is radiosensitive at the same time [9]. Anastomosis of the central airways should be done by single stitches going through all layers of the intercartilaginous area. Some surgeons prefer vicryl for anastomosis of the cervical trachea. For the remaining resections most surgeons choose PDS (e.g. 2-0–4-0). Using Prolene should be avoided due to its tendency to granulation formation. A stay suture can be placed at the transition zone between pars cartilaginea and pars membranacea before suturing of the anastomosis. Preliminary placing of the stitches begins at the front wall from posterior to anterior without tying them. Subsequently, same procedure is performed at the pars membranacea. The knots are tied extraluminally. To facilitate this step, airway tube can get removed and further ventilation ensured by endotracheal jetventilation. Optimal sealing of the anastomosis is evaluated by water test.

For reconstruction, the individual shape and location of the aortic arch has to be taken into account. The mobilization of the left main bronchus after resection of a long tracheal segment can be difficult despite previous division of the Botalli ligament. A direct anastomosis of the right main bronchus to the trachea with consecutive end-to-side connection of the left main bronchus to right bronchus intermedius is an option for this challenge, preferably performed through a sternotomy. For parenchyma-sparing, isolated resection of the bifurcation, the reconstruction is achieved by side-to-side anastomosis of both main bronchi and construction of a neocarina [10, 11]. Subsequent connection of both main bronchi to the trachea is performed by end-to-end technique with single stitches. Thereby, it must be considered, that the mobilization of the left main bronchus is limited also in this situation because of its relation to the aortic arch. To achieve a tension-free anastomosis it may be necessary to perform a bronchoplasty with implantation of left main bronchus to the right bronchus intermedius, after anastomosis of the right main bronchus to the trachea is finished.

Direct anastomosis of the left main bronchus to the trachea and consecutive implantation of the right main bronchus laterally into the distal trachea is another technique. Thereby, another gain of about 2–3 cm distance is possible.

The ventilation management of these reconstruction procedures is challenging, but thanks to their successful further development, extra-corporal oxygenation is rarely necessary. A bronchial lavage is performed at the end of the operation in order to clear the lungs from mucus and blood cloths. Extubation of the patient should be done as soon as possible in order to protect the anastomosis from excessive pressure and after that the patient is usually transferred to a surveillance unit or intermediate care unit in spontaneously breathing condition. Prolonged postoperative ventilation significantly increases morbidity and mortality rate [12].

Post-operative management

As mentioned above, the patient should be extubated immediately after the operation. The positive pressure ventilation can apply stress on the airway anastomosis and increase postoperative morbidity. Heavy stitches between the chin and the upper part of the chest are optional, depending of the length of the resected airway part, and are used to maintain a mild degree of cervical

flexion and to avoid uncontrolled head and neck movements, which could overstretch the anastomosis in the early post-operative period. The chest tube and the stitches are usually removed on post-operative day 2–3 and 5, respectively. Many surgeons perform a bronchoscopic check of the anastomosis before discharge [13]. The first follow-up of the patient could be scheduled after 1 month with chest X-Ray and bronchoscopy. Based on tumor histology and the pathological staging the patient is referred to the oncologist and/or radiotherapist for the further medical treatments.

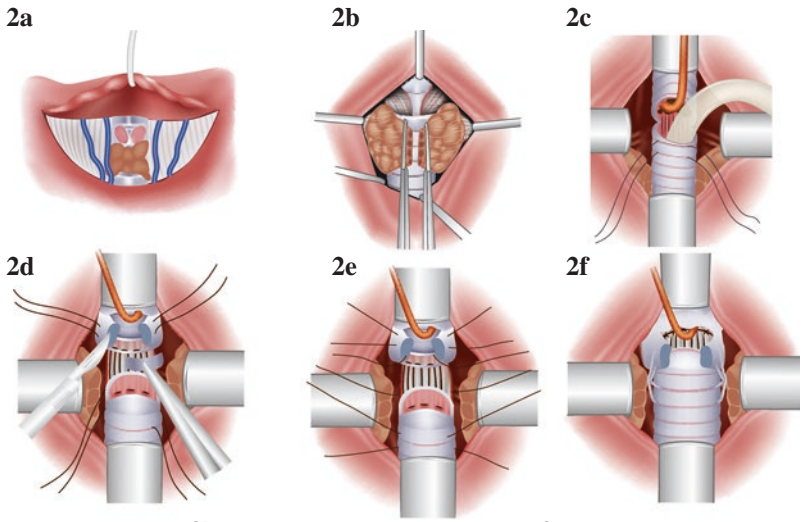
Cervical Trachea's Pathology—Techniques

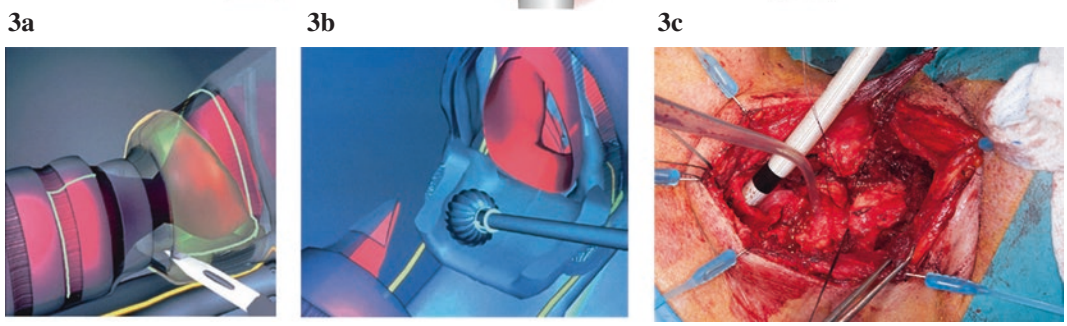
Subglottic tracheal stenosis is one of the most challenging problems in tracheal surgery. It is essential that the patient's general condition is optimized before surgery is attempted. The rules for temporarily securing the airway and preparation of the patient are the same as for intrathoracic tracheal resections. The patient is placed in a supine position. A classical or a caudally curved Kocher incision is made over the surgical site (Pic 2a). Subplatysmal flaps are developed to the level of the thyroid cartilage and sternal notch, and the strap muscles are separated in the midline and retracted laterally to expose the thyroid gland. The thyroid (Picture 2b) isthmus is clamped and divided, and both of its ends are oversewn with a suture; this exposes the whole cervical trachea and lower part of the larynx. The trachea is dissected circumferentially at the level of the distal end of the stenotic segment. The dissection plane is kept strictly on the airway to avoid injury to the laryngeal recurrent nerves. This dissection may be difficult due to fibrosis or scarring resulting from a previous tracheostomy, and requires caution and patience. The dissection should not be extended to far posteriorly in order to avoid damage to the vascular supply of the trachea. The cuff of the endotracheal tube is deflated and the anterior wall of the trachea is divided at the distal end of the stenosis, which is determined by bronchoscopy. If the extent of stenosis is difficult to determine, it is safer to transect the trachea through the stenotic segment and then extend the resection under direct visual control (Picture 2c / 2d). A suture is fixated to the tip of the endotracheal tube, before it is subsequently redrawn; the fixation suture (Picture 2e / 2f) can be used at a later stage of the procedure to easily pull the endotracheal tube caudally and placing it distal to the anastomosis. Next, cross-field ventilation is started using a sterile armored endotracheal tube (reinforced with metal coils—this prevents obstruction of the tube even with excessive kinking of the tube), which is placed in the distal trachea. This tube is removed intermittently during the procedure in order to allow for a better exposure of the posterior tracheal wall. In the distal part of the airway, the membranous wall of the trachea is divided cranially to the level of transection of the cartilaginous wall, so that a flap of the membranous part is created. If there is still stenosis of the distal trachea, resection of its cartilages is extended until normal (or near normal) tracheal cartilage and mucosa area reached.

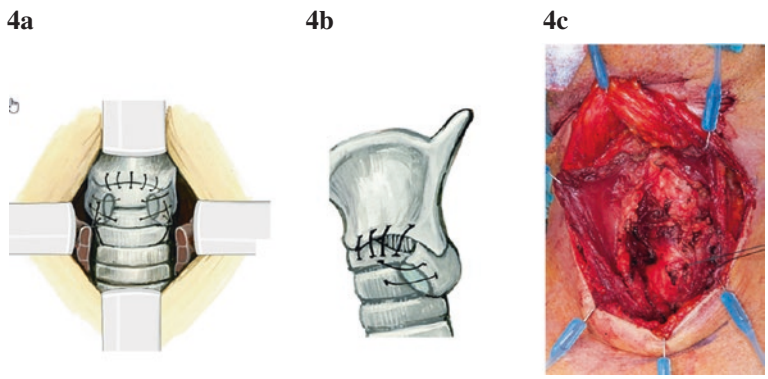
Cricotracheal resection

The line of transection of the cartilage is slightly oblique, being in the midline approximately one ring higher than at the junction with the membranous wall. Two traction sutures are placed in the mid-lateral wall of the trachea, one ring distally from the transection line. The anterior wall of the cricoid (3 a/b/c) cartilage is excised and the lumen of the subglottic larynx is enlarged by the removal of fibrotic, thickened mucosa from the posterior wall of the cricoid cartilage. This denuded part of the cartilage will be covered with the flap of membranous tracheal wall at a later stage of the procedure. Two traction sutures are placed in the stumps of the cricoid cartilage. For suturing of the anastomosis most surgeons prefer using PDS, but some also use Vicryl. It starts with a line of interrupted sutures, for example with PDS 3-0, placed through the base of the flap of membranous tracheal wall and the lower border of the cricoid cartilage. After all of these sutures are placed, the patient's neck is flexed, the trachea and the larynx are approximated by pulling and tightening the stay sutures, and this first line of anastomotic sutures is tightened. Next, a second line of sutures is placed,

fixing the apex of the membranous flap to the posterior laryngeal wall at the level of the upper border of the cricoid cartilage, using for example PDS 5-0. Tightening of these sutures completes the posterior part of the anastomosis. By pulling the fixation suture of the endotracheal tube, the tube is brought into the filed, the suture is removed, and the tube is advanced into the trachea distal to the anastomosis. Next, the anterior part of the anastomosis is completed by placing sutures through the tracheal rings, stumps of the cricoid cartilage and thyroid cartilage with for example PDS 3-0 (4a). Oblique transection of the trachea allows (4b) better adaption to the geometry of the transected subglottic larynx (4c). Saline is poured into the wound and the anastomosis is checked for air leak. Fibrin glue can be applied to the anastomosis to close small irregularities of the anastomosis. In addition the strap muscles are approximated in the midline to buttress the anastomosis, and the wound is closed in layers.







Thoracic Trachea's Pathology—Techniques

If necessary, the airway can be opened temporarily by rigid bronchoscopic dilation, providing that only a short period of time (i.e. weeks) is needed before definitive treatment. The use of bronchoscopic laser treatment to restore airway patency should be avoided if definitive resection is anticipated as it further injures the airway. Similarly, self-expanding metallic stents should not be used as they increase the extent of airway injury, often necessitating a longer resection, which again is associated with a far higher rate of failure.

In general, definitive tracheal resection and reconstruction should be considered in all patients with obstructive airway symptoms and airway stenosis after ventilation if they have a favorable anatomy. Absolute contraindications are few, and include:

- Non-reconstructable airway (excessively long segment of damaged airway).
- Severe comorbidities.
- Continued need for ventilation.

Relative contraindications include:

- History of radiation to the trachea.
- Active steroid use.

Virtually all operable patients with postintubation tracheal stenosis can be approached by a simple small cervical collar incision.

The extent of safe tracheal resection and reconstruction is influenced by anatomic and demographic factors. The most important factor is probably the body habitus; young, tall, thin patients with long necks have an abundance of trachea and are the best candidates for this type of surgery. On the contrary, elderly, kyphotic, short, obese patients with short, wide necks and a cricoid cartilage that is at the sternal notch are the most challenging candidates. Recent high-dose steroid use and insulin-dependent diabetes mellitus seem to be risk factors for anastomotic problems, so special attention needs to be paid to the details and amount of tension on the anastomosis. Pediatric patients tolerate anastomotic tension less well than adults; ideally, resections of only <30% of the length of the trachea should be performed in children, whereas some adults can tolerate resections of up to 50% of tracheal length. It has to be noted, that previous tracheal surgery causes relative fixation of the remaining trachea and thus limits any possible re-resection to less than standard. Previous radiation therapy to the trachea limits tracheal mobility and impairs microvascular blood supply, both of which place constraints on how much of the trachea can be removed safely.

Bronchoscopic examination is the first-line intervention for the assessment and treatment of airway obstruction. Patients who present with critical airway obstruction can almost always be managed with bronchoscopic dilation. Rigid bronchoscopy has several advantages over flexible bronchoscopy due to its superior ability to provide airway stabilization, tissue diagnosis and precise evaluation prior to other interventions.

In most cases, tracheal tumors are resectable by an experienced airway surgeon. A resection of <4 cm is associated with favorable results, but occasionally segments up to 6 cm long can be resected if the patient is an otherwise excellent candidate.

Tumors in the upper third of the trachea are approached by a cervical (5a) collar incision, those located in the middle third by a combined cervical and mediastinal incision (a collar incision followed by a partial upper sternotomy), (5b) and tumors in the lower third usually by a right thoracotomy in the fourth intercostal space (6). Occasionally, tumors that involve a long segment of the trachea, extending down close to the carina, are resected by a full sternotomy, so that bilateral hilar releases can be done, realizing that access to the anastomosis will be somewhat more challenging.

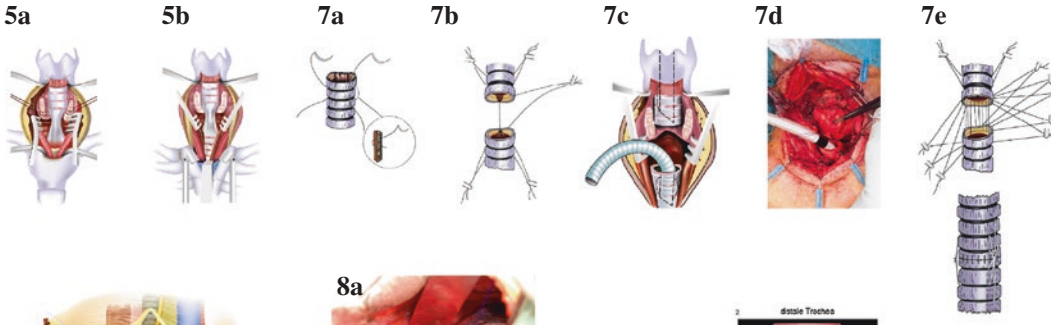
The trachea is dissected circumferentially to the determined distal transection point, staying directly on the trachea to avoid injury to the recurrent laryngeal nerve. This nerve is never dissected out and, in fact, is almost never seen.

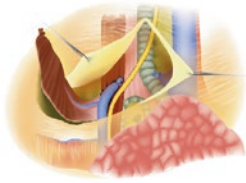
Typically, two rings distal to the true division point are dissected so that there is enough space to suture the anastomosis. It is important not to dissect too far beyond the proposed division site as doing so would devascularise the trachea. If the distal extent of the stenosis is unclear from an external view, it is advisable to perform bronchoscopy. In this way, the trachea can also be transilluminated or a needle can be passed through its anterior wall in order to define the true limits of the stenosis. The trachea is divided transversely, usually at the proximal extent of the pathology. Once the proximal trachea has been divided, the two lateral walls can be grasped with Allis clamps and elevated to allow easy dissection of the posterior membranous wall from the esophagus. The distal tracheal division is then completed and the specimen removed.

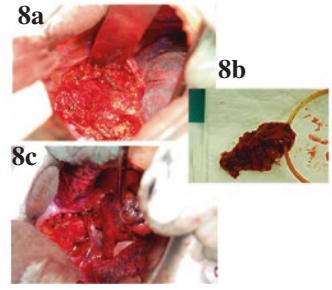
Stay sutures of 2-0 Vicryl (7a) are placed at 3 and 9 o'clock at the proximal and distal edges of the divided trachea. They are placed at least one ring away from the edge and around at least one whole ring so they will not cut through the tracheal wall. These stay sutures will be tied first (knots outside!) when the anastomosis is approximated and used to take the tension off the true anastomotic sutures. The anastomosis is started in the posterior midline with fine 4-0 Vicryl sutures (7b). The anastomotic sutures by convention are placed so that the knots will ultimately be on the outside of the airway. For careful and precise placement and proper spacing to address any size discrepancies, intermittent periods of apnea by removing the cross-field endotracheal tube are helpful (7c / 7d). The sutures are placed 3–4 mm in depth with 3–4 mm distance between each suture [8]. Since the sutures are only positioned in a first step and not directly tied, they can for example be held with small hemostatic clamps and clipped to the surgical drapes in a circumferential fashion so that they remain organized (7e). They will be tied in reverse order of placement: the anterior sutures first, followed by the lateral and then the posterior sutures. While the sutures are placed the airway is constantly suctioned by an assistant in order to prevent blood from entering the distal airway; this is especially important prior to re-approximation of the airway. The endotracheal tube is advanced into the distal trachea and the cuff is re-inflated gently. After the anastomosis is completed, a leak test is performed to ensure that it is airtight. For anastomosis of the upper third of the trachea (e.g. postintubation tracheal stenosis), the thyroid can be used for anastomosis coverage by re-approximating the divided thyroid isthmus. If the anastomosis is lower and adjacent to the brachiocephalic trunk, a strap muscle can be mobilized and interposed between the brachiocephalic trunk and trachea to minimize the risk of a fistula. For a distal tracheal resection with a thoracotomy approach, a pericardial fat pad, an intercostal muscle flap or the mobilized azygos vein can be wrapped around the anastomosis (Pic 8a/b/c/d). A guardian chin suture can be placed from the undersurface of the chin to the anterior chest with heavy suture material to prevent hyperextension of the neck. Immediate postoperative extubation should be attempted whenever possible. Control bronchoscopy is usually done on the 5th postoperative day to ensure proper healing of the anastomosis. Separation, necrosis and granuloma formation are especially looked for during control bronchoscopy. If anastomotic healing is unproblematic at this point, the occasional chin stitch is usually removed at this point.

Final air leak check should be performed also for anastomosis of the lower trachea with positive airway pressure of 20–30 cm H_2O (with the endotracheal cuff deflated) whilst the anastomosis is submerged under saline. If there are any small leaks, an additional suture should be placed to correct this. In addition, bronchoscopy is performed (with the endotracheal tube withdrawn under direct bronchoscopic control) to visually inspect the anastomosis from the inside for technical problems, such as loose sutures, inadequate approximation or an inadequate airway (luminal diameter).

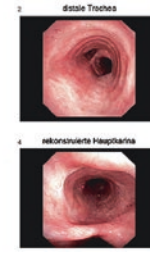
Patients with narrow or positive margins are usually referred for adjuvant radiation but only after bronchoscopy 1–2 months following resection has demonstrated a well-healed anastomosis.



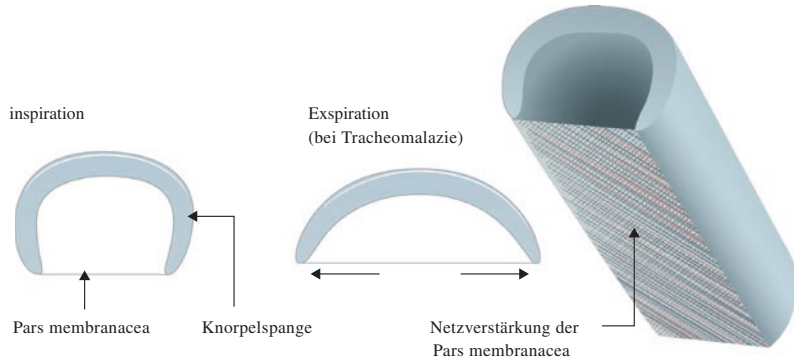




Picture 6: View through the right thoracotomy to the mediastinum and the airway structures



8d: Distal trachea after reconstruction of main carina



Picture 9: Reinforcement of the Pars membranacea with prolene mesh

For definitive surgical treatment of tracheomalacia or tracheabronchomalacia, trachea- and tracheobronchoplasty is the procedure of choice. Via posterolateral thoracotomy, a polypropylene mesh is attached from behind to the pars membranacea and fixed at its sides to the cartilaginous part (Pic 9). After adhesive remodeling processes, a dorsal reinforcement is achieved, which counteracts the tendency of the trachea to collapse. In localized tracheomalacia, resection of this segment is another treatment option. So far, there is still no completely established option for an tracheal replacement by foreign materials, nonviable tissue, tissue engineering, or transplantation [14], but current developments in this field are promising [15–19].

Self-study

(1) Which mobilization technique is, in general, the most efficient one?
   (a) Mobilization maneuver according to Montgomery.
   (b) Mobilization of the aortic arch and dividing of the Botalli ligament.

(c) Moblization maneuver according to Macchiarini.
(d) Flexion of the head.

(2) Which contraindications for tracheal surgery would you consider important?
1. Age and sex.
2. Steroid use.
3. Continued need for ventilation.
4. Long segment of a damaged trachea to resect.
5. History of radiation to trachea.

(a) 2 + 3 + 5.
(b) 3 + 4.
(c) 4.
(d) 1 + 4 + 5.

Answers
(1) d.
(2) b.

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Tracheal Resections—Intraoperative Accidents and Complications

Patrick Dorn and Gregor J. Kocher

Key Points

1. Knowledge of the anatomy of the trachea and the central bronchial airways, as well as the relations between its adjacent structures and understanding of pathophysiologic influences of different pathologic conditions are of vital importance for the surgeon in order to allow for an adequate evaluation of the treatment, operability, and technique of resection.
2. Tumors of the trachea or the central bronchial system are rare and primary tracheal tumors are potentially curable by resection.
3. The most frequent etiology of non-neoplastic tracheal stenosis is the post-intubation stenosis. Far less frequent are post-traumatic, congenital, inflammatory/infectious stenosis or stenosis due to extrinsic compression, e.g. goiter or acquired vascular lesions.
4. Anesthetist and surgeon have to be a well-established team to offer the patient a maximum of safety during surgery.
5. Reconstruction of the airway can be performed in different ways according to the extension of the resection and according to the experience of the surgeon with the aim of obtaining a tension-free anastomosis, which subsequently reduces the possible the risk of post-operative complications due to healing problems.

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To optimally prepare and stabilize the patient for such an operation, sometimes the intraluminal part of the tumor has to be at least partially resected by means of rigid bronchoscopy in the preoperative setting to prevent any respiratory problems during anesthesia and allow to secure the airway for surgery in the first place. Additionally, an instruction for respiratory exercises and training for effectively coughing up secretions should be performed already in the preoperative period [1]. Postoperative respiratory exercises, timely mobilization of the patient and restrictive fluid intake are important factors in the immediate course after surgery.

Generally, it can be stated that, with increasing length of resected airway, also postoperative morbidity, mortality and the rate of anastomotic complications increase [2]. The perioperative mortality after resection of the tracheobronchial bifurcation is relatively high, ranging from 2.5–15% [3–6]. The most frequent complications after tracheobronchial resections are retention of sputum, delayed healing of the anastomosis, pneumonia, lymphostasis and supraventricular arrhythmias. Uni- or even bilateral paresis of the

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recurrent laryngeal nerve is also a possible complication. The most severe and life threatening complication of central airway surgery is acute respiratory distress syndrome (ARDS). Its incidence is reported to be around 20% after resection involving the carina. It is associated with a mortality rate of about 50 to 100% [4, 6, 7].

For prevention and management of complications, the early use of bronchoscopy is important for bronchial lavage and monitoring of the healing of the anastomosis. Blind endoluminal aspiration is obsolete and should be avoided to reduce the risk of mucosal lesions at the region of previous resection. Postoperative hemoptysis and/or abnormal foetor ex ore have to be evaluated immediately by bronchoscopy.

Outcome and Follow-up After Central Airway Resection

Grillo's large series of 503 patients who underwent segmental tracheal resection for postintubation stenosis shows a good to satisfactory postoperative result in 94% of patients (471/503 cases) [8]. The results were classified as 'good' if the patient could play sports without exertional dyspnea, and 'satisfactory' if the patient could perform normal activities but was stressed on exercise. These results are in accordance with smaller reported series of tracheal resections with end-to-end anastomosis in adults [9–12]. Failure occurred in 20 (3.9%) and death in 12 (2.4%) of cases.

Depending on the histology of the primary tracheal tumor, 5-year survival rates between 39 and 47% can be expected in case of squamous cell carcinoma and between 52 and 100% in adenoidcystic carcinoma [3, 13–15]. The outcomes after primary radiation therapy are reported to be significantly worse compared to surgical resection [16, 17]. Endoscopic ablation only has a palliative effect with the aim of reducing tumor obstruction and associated dyspnea.

Indications for resections of the tracheobronchial bifurcation are mostly for non-small cell-lungcancer cancer infiltrating the carina. 5-year survival rates of these T4-tumors vary between 26.8 and 42% [5, 18–20]. Survival seems to dependent largely on mediastinal lymph node-staging. While for N0- and N1-status the 5-years survival rates range from 44.4 to 83%, the long-term survival decreases in N2- and N3-situations to around 0–15% [6, 7, 21]. Despite the long-term survival is influenced by different factors and the presence of positive N2 disease per se is not a definitive contraindication for radical treatment, a carinal resection should be weighed up carefully in this situation. After resection of the bifurcation for adenoidcystic carcinoma and carcinoid tumors, 10-years survival rate increases up to 69–100% [7].

The follow-up strategy is similar to that of primary bronchial carcinoma with a structured after-care concept over 5 years postoperatively. In addition to follow-up CT scans, endoscopic check-ups should be performed semi-annually in the first 2 years and annually in the remaining 3 years after resection.

Epidemiologic studies suggest that at least half of all patients with primary tracheal carcinoma are surgical candidates, which would be far more than actual resection rates show. This discrepancy could be based on patient selection, but also due to a lack of knowledge and centers with multidisciplinary experience in the treatment of tracheal tumors [17, 22].

Minimal-Invasive Approaches to the Trachea and Central Airways

During the last two decades, minimally invasive surgical techniques are increasingly used worldwide in the field of thoracic surgery and other specialties due to important advantages such as lower complication rates, less pain, shorter hospital stay and even a trend versus better survival for early stages of non-small cell-lungcancer cancer (NSCLC). This technical step forward encouraged further development and motivated many surgeons to reschedule most open procedures as VATS resections [23]. Nevertheless, when compared to thoracotomy, VATS procedures turn out to be more technically

demanding, mainly because of the transmission from an operating field with multiple angle and especially instrument options and with direct view, into a two-dimensional flat screen with limited access to the operation site.

Tumors invading the distal trachea or carina additionally represent a challenge due to the complexity of airway reconstruction and management through a thoracoscopic approach. Furthermore, sufficient oxygenation of the patient has to be maintained at any time during surgery. Generally, it seems that, with improvements in VATS competency, greater exchange of knowledge and technical know-how, and advances in equipment, increasing number of centers are able to perform such extended operations by a thoracoscopic approach [24, 25]. Thanks to a promising evolution of VATS techniques and even of devices, as for example endoscopic knot tying devices or barbed suture technology for bronchial anastomosis, further improvements can be expected in the near future [24, 26, 27]. The reduction of anastomotic tension and the right choice of the type of reconstruction are the two main concerns when dealing with tracheal and/or carinal reconstruction, regardless of the approach (open or VATS) [18, 26, 28].

Numerous studies, although mostly retrospective, were able to show a significant benefit of VATS over open surgery concerning acute postoperative as well as chronic pain and/or numbness at the thoracic incision site [29]. Recently also randomized controlled studies reported a reduction in postoperative pain, and significantly better self-reported quality of life during the first year after surgery when a minimally invasive approach was used [30]. Another rapidly developing and increasingly used technique is single-port (uniportal) VATS, which holds great promises in further reducing surgical access trauma and postoperative discomfort. The involvement of less intercostal spaces further reduces postoperative chest wallwall pain, complications and length of hospital stay compared to standard 3-port VATS [31, 32].

In the end, these technically demanding operations remain challenging despite of the operative approach used for it, associated with acceptable but also significant morbidity and mortality. Careful preoperative evaluation is the key factor, not only for successful resection and reconstruction, but also for improving postoperative outcomes. Therefore, patients with thoracic malignancy involving the carina or distal trachea should be evaluated as possible surgical candidates based on disease extent and functional status. The minimally invasive approach seems to be a promising option for these resections in the hand of experienced VATS-surgeons, but future studies are needed to further evaluate the safety and especially morbidity rates as well as long-term outcomes after such minimally invasive approaches.

Self-Study

(1) Which complication/-s is/are seen after tracheobronchial resection?
   1. Retention of sputum
   2. Delayed healing of the anastomosis
   3. Lymphostasis
   4. Supraventricular arrhythmias
      (a) 1+3+4
      (b) 1+2+3
      (c) 2+3+4
      (d) All of them

(2) What is the expected benefit of a Video Assisted Thoracic Surgery (VATS) resection for central airway tumor?
   (a) Less pain
   (b) Lower mortality rate
   (c) Better visualization for complete tumor resection
   (d) Reduced need for preoperative evaluation

Answers

(1) d
(2) a

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Embryology of the Lung

Sergio B. Sesia and Gregor J. Kocher

Key Points

1. The respiratory system origins from the anterior foregut endoderm.
2. The conducting airways are formed first, followed by the development of alveoli.
3. By branching morphogenesis, lung buds generate an arborized airway tree.
4. During the canalicular stage (week 16–26) the first blood-air barrier is formed and survival becomes possible.
5. Alveolarization continues until adulthood.

Introduction

The main respiratory tract extends from the larynx, to the trachea, the stem bronchi and down the lungs. The upper extension of the respiratory tract furthermore includes the nose, the paranasal cavities and the pharynx. The main function of the lungs is to supply oxygen to the cells of the body and to remove carbon dioxide produced by cellular metabolism. Therefore, the lungs participate in the acid-base balance. In case carbon dioxide is insufficiently expelled through the lungs, it may become toxic and cause convulsions, unconsciousness, and eventually death. With each breath, the lungs get in contact with microorganisms and other pollutants, subsequently developing an adaptive immune response. Finally, lung cells guarantee energy and nutrients for their own maintenance by metabolizing substrates.

To achieve these goals, the lungs have evolved to a vast network of ramified epithelial and vascular structures that lead to the alveoli, the gas-exchanging units.

This chapter focuses on the description of the different stages of lung development.

During the embryonic development in the third week, the embryo develops from three different germ layers, the ectoderm, the mesoderm and the endoderm. From the endoderm arises gradually the primitive gut tube, the foregut, the lung and the trachea.

The lung development is subdivided into three main stages that overlap: the embryonic, the fetal and the postnatal stage. The lung organogenesis is part of the embryonic period. The fetal lung development includes the pseudoglandular, the canalicular and the saccular period. Continued alveolarization and microvascular maturation belong to the postnatal period.

The inner surface of the lung is formed by morphogenesis and septation, also called alveolarization [1]. The two lung buds grow from the center to the periphery by branching into the surrounding mesenchyme and by doing so,

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finally building all the airways. This mechanism of branching morphogenesis is responsible for the formation of approximately 10% of the gas exchange surface area [1]. The remaining 90% are formed by alveolar septation during which alveoli and bronchioli are subdivided [2]. This process is followed by the stage of microvascular maturation during which alveolar septa are thinned and the microvasculature is maturating. According to novel beliefs, this maturation continues until young adulthood.

Embryonic Period (Weeks 4–7)

At 4–6 weeks postmenstrual age or day 26 post conception, the lung formation begins. The primitive lung originates from the laryngo-tracheal groove of the anterior part of the primitive foregut. A patch of the anterior foregut endoderm is budding and forms the lung primordium (Fig. 1). This is followed by a subdivision into the two main bronchi. Subsequently, both lung buds begin a repetitive bifurcation process, called branching morphogenesis that ends in a bronchial tree [2], enclosed by mesenchymal cells. Esophagus and trachea arise from the septation of the primitive foregut (Fig. 2), and the tracheal cartilage rings from the enclosing mesenchymal cells. At the end of the embryonic period, the visceral and the parietal pleura emerge from the mesoderm. The visceral pleura starts to compartment the heart from the lungs and to separate the lungs into lobes [3].

Retinoic acid seems play a central role in the branching morphogenesis process, which is regulated by a network of different factors like transforming growth factor β, fibroblast growth factor 10, Sonic Hedgehog, and Wingless/Integrated [4].

Same as the cartilage rings, the pulmonary vessels arise from surrounding mesenchymal cells by angiogenesis. The development of the vessels runs parallel to the evolution of the airways.

Abnormalities during the embryonic period may lead to high postnatal morbidity, such as diaphragmatic hernia, pulmonary hypoplasia, tracheo-esophageal fistula, and esophageal atresia.

Pseudoglandular Stage (Weeks 7–17)

The branching process, which started during the embryonic period, continues throughout the pseudoglandular stage, running until the end of week 17. This highly regulated process

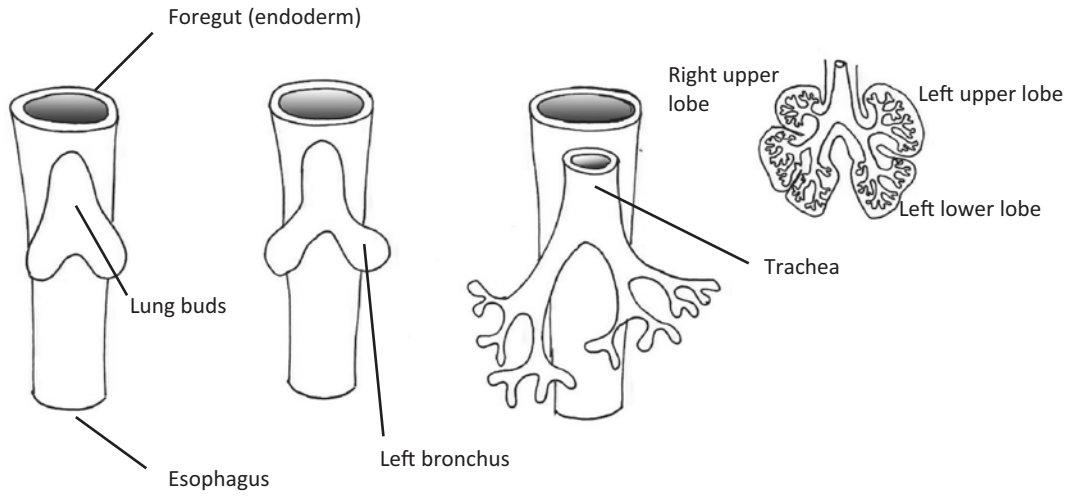

Fig. 1 Schematic representation of budding of the endoderm into two main bronchi (left pictures) with the start of the bifurcation process (right pictures) (adapted from [18])

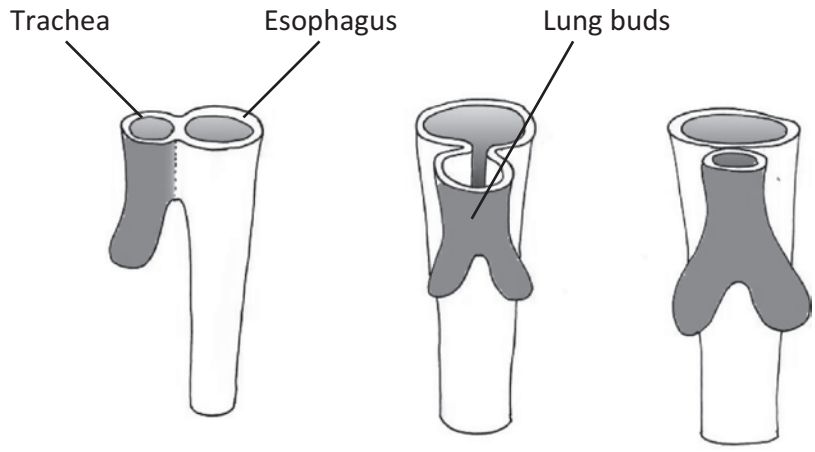

Fig. 2 Septation of the trachea from the esophagus (adapted from [19])

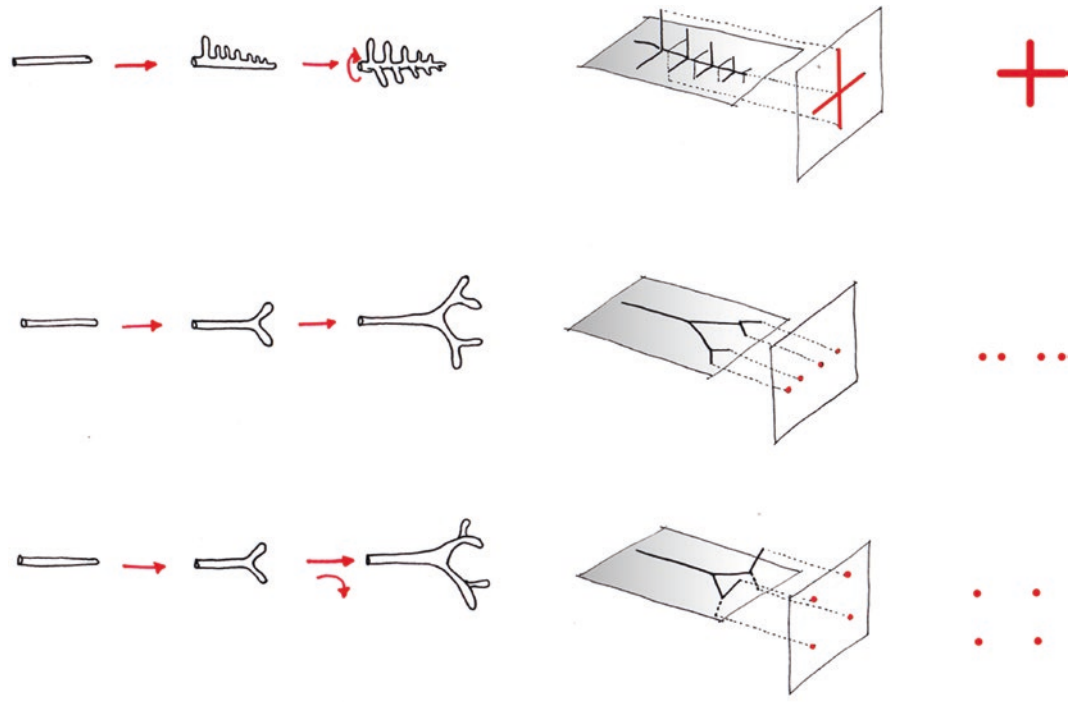

Fig. 3 Different modes of lung branching: domain branching (upper picture), planar bifurcation (centre picture) and orthogonal bifurcation (lower picture) (adapted from [20])

finally results in the generation of a bronchial tree, arising from three different branching modes (Fig. 3): in the so called "domain branching", daughter branches or new lung buds form on both sides to the main branch. In the "planar bifurcation" branching occurs in the same plane, in the orthogonal bifurcation branching is orthogonal to the first plane [5]. During the pseudoglandular stage, 16–25 generations of future airways are formed and

the vascular development is completed [6]. It is also during this stage that first ciliated, goblet and basal cells as well as alpha-smooth muscle cell appear in and around the proximal airways. The movement of those contractile muscle cells is supposed to stimulate and pilot the branching morphogenesis [7]. Stretching of the muscle cells and first fetal breathing movements starting around week 10, stimulate the epithelial cell proliferation and the secretion of surfactant lipids by type II epithelial cells [8].

Formation of bronchial airways is completed by 16 weeks. After that, further growth occurs by widening and elongation of existing airways. According to Weibel, the first 16 generations of primitive airways constitute the conducting airways, the last 7, the respiratory zone [6]. Alveoli start appearing at generation 17.

Failure in the branching morphogenesis of a polycystic kidney may lead to an oligohydramnion, which also affects the lung development and therefore causes pulmonary hypoplasia [9].

Canalicular Stage (Weeks 16–26)

During this stage, thousands of terminal branches are formed to evolve to bronchioli and alveoli. Cuboidal cells differentiate into type 1 and type 2 alveolar epithelial cells. Type 1 cells line the alveoli and by coming in close contact with the mesenchymal capillary network form the first blood-air barrier. The type 2 cells begin to produce and secrete the surfactant in week 22–24. The surfactant decreases the surface tension at the air-blood barrier and therefore facilitates lung expansion.

During the canalicular stage, also the bronchoalveolar duct junction is formed, which represents a stem cells niche [10]. In this area ciliated and Club cells or Clara cells are transformed to type I and type II alveolar epithelial cells [2]. During lung development the bronchoalveolar duct junction remains at the same generation initially formed [11].

An insufficiency of surfactant and gas exchange surface may lead to a respiratory distress syndrome in new-borns, also called hyaline membrane disease. Very immaturely born infants at this time may survive, but require surfactant and mechanical ventilation assistance in a neonatal intensive care unit.

In case of reduced capillary density and air-blood interface, alveolar capillary dysplasia may result. This condition is characterised by misalignment of the pulmonary veins, thickened alveolar septum and pulmonary hypertension, and represents a lethal congenital lung abnormality [12].

Saccular Stage (Weeks 24–38)

This intermediate stage lies between the end of the branching morphogenesis and the beginning of the alveolarization. During the canalicular and saccular stages terminal branches form epithelial sacs and the future alveoli that are fully matured only during the alveolarization stage.

The terminal airways are widening and form sacculi. By condensation of the mesenchyme immature interair, septa are formed and double-layered by a capillary network. The septa are lined to approximately 90% by type I and to approximately 10% by type II epithelial cells and smooth muscle cells.

Interestingly, branching morphogenesis and alveolarization are programmed differently from a genetic point of view [13].

Alveolarization (Week 36 to Adulthood)

Secondary septation of alveolar ducts into alveoli and pulmonary angiogenesis, allowing to enhance the gas exchange area of the lungs, occur during the alveolarization stage. This full maturation of the alveoli starts before birth. Interestingly, contrary to earlier believing, alveolarization continues after birth. Alveoli prior to birth account for approximately 50 million, while there are around 300 million in an adult lung. More than 85% of the alveoli are formed after birth [14]. Thus, two different alveolarization methods have been described: the classical and

the continued alveolarization [14]. The increase of alveoli is less significant during continued than during classical alveolarization. During the classical alveolarization, which takes place from week 36 prior to around 3 years after birth, immature septa containing a thick double-layered capillary network mature by microvascularization and apoptosis of interstitial cells to form matured septa consisting of one capillary layer and a thin blood-air barrier to enhance the gas exchange.

The hypothesis of remodelling and repair of lung parenchyma at any age support the concept of continued alveolarization. While glucocorticoids administered during classical alveolarization inhibit the alveolarization, retinoic acid given during continued alveolarization may reverse this trend [15]. In animals, glucocorticoids administered after birth have been shown efficient to treat an impaired lung. The grade of recovery was dependent on the length of treatment [2]. The human lung is able to form new alveoli as long as it grows. Recovery of impaired lung by bronchopulmonary dysplasia has been reported [16]. Even, compensatory lung growth with formation of new alveoli after lobectomy was described [17]. Those compensatory repair mechanisms seem to be active only during continued alveolarization. But, it is unknown how long exactly persists the continued alveolarization and how to reactive it in order to treat lung diseases such as fibrosis, emphysema or chronic obstructive pulmonary disease.

Conclusions/Summary

The understanding of physiological and pathological lung development and their molecular mechanisms is still limited. Methods to control alveolarization and microvascularization may establish new treatment options for chronic lung diseases. But, prior to this, a better comprehension of the lung structure (possibly by new imaging methods) and of the metabolic pathways is required.

Self-study
Which statement is true

(a) The formation of alveoli is completed at week 37.
(b) *Oligohydramnion may cause pulmonary hypoplasia.*
(c) During the pseudoglandular stage, the branching process begins.
(d) Trachea and esophagus arise from mesoderm.
(e) Alveolarization begins already during embryonic stage.
(f) Abnormalities during septation process may lead to esophageal atresia.
(g) The septa between the alveoli consist of 10% type I epithelial cells.
(h) *Alveolarization is not completed at birth and continues at least during adolescence*.

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Congenital Malformations of the Lung

Bernd Pösentrup, Andreas Leutner, Jens Guenter Riedel, and Martin Reichert

Key Points

- Resection prior to symptoms needs to be achieved.
- CT scan adds valuable information about the types, location and vascular supply of the malformation.
- VATS Lobectomy is feasible and safe.
- Compensatory growth of the remaining lung prevents loss of pulmonary function in children operated younger than 5 years of age.

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Introduction

Genesis of the congenital malformations or lesions of the lung is either a (subtotal) closure or atresia of the connective bronchus to the tracheobronchial tree, a topical embryonal maldevelopment of the lung tissue in embryos or a vascular malformation or extraanatomical vascularization to the maldeveloped lesion [1]. Different entities of lung malformations in children are known, whereas mixtures of all of these entities have been described in the current literature [2].

Congenital malformations of the lung can be basically categorized into:

- Congenital lobar emphysema.
- Bronchial atresia and bronchogenic cyst.
- Bronchopulmonary sequestration.
- Congenital pulmonary airway malformations (CPAMs).

The specific therapy of congenital malformations of the lung in the prenatal and perinatal period or childhood should be reserved for specialized centers with broad experience and should be discussed in a multidisciplinary team of pediatric surgeons, neonatologists, radiologists and obstetric gynecologists specialized in prenatal diagnosis. We herein describe the characteristics, diagnosis and therapeutic approaches of these most relevant congenital malformations

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of the lung, based on current evidences and clinical practices.

Congenital Lobar Emphysema

In congenital lobar emphysema (CLE) intrinsic (bronchomalacia, mucosal ectopy or stenosis) or extrinsic (vascular malformation, tumors e.g. bronchogenic cysts) factors lead to a subtotal closure of the bronchus and valve gear effect with air trapping and volume trauma of the affected lobe. Prevalence is about 1 in 20,000–30,000 births [3]. Most commonly the upper lobe is affected, but principally the congenital lobar emphysema can affect more than one pulmonary lobe. Since the fluid produced by the lung in utero is able to pass by subtotal stenosis, CLE unusually becomes evident until the first days of a new born, but most commonly during the first six month of life [4]. Typical symptoms are dyspnea and recurrent pulmonary infections caused by the space-consuming character leading to atelectasis of the healthy lung, displacement of capable lung tissue and mediastinal shift (Figs. 1 and 2). The adequate prenatal diagnosis by ultrasound is difficult, in some cases a lobar emphysema impresses as an echogenic homogeneous tumor [5].

Bronchial Atresia and Bronchogenic Cyst

In cases of bronchial atresia (BA), the total obstruction of a peripheral bronchus encloses the fluid produced by the lung. Ongoing pregnancy comes along with decreased lung fluid production, size reduction of the BA and growing of the capable lung [6, 7]. Typically peripheral BA occurs by pneumonia beneath the baby period (median age of occurrence 4, 2 years).

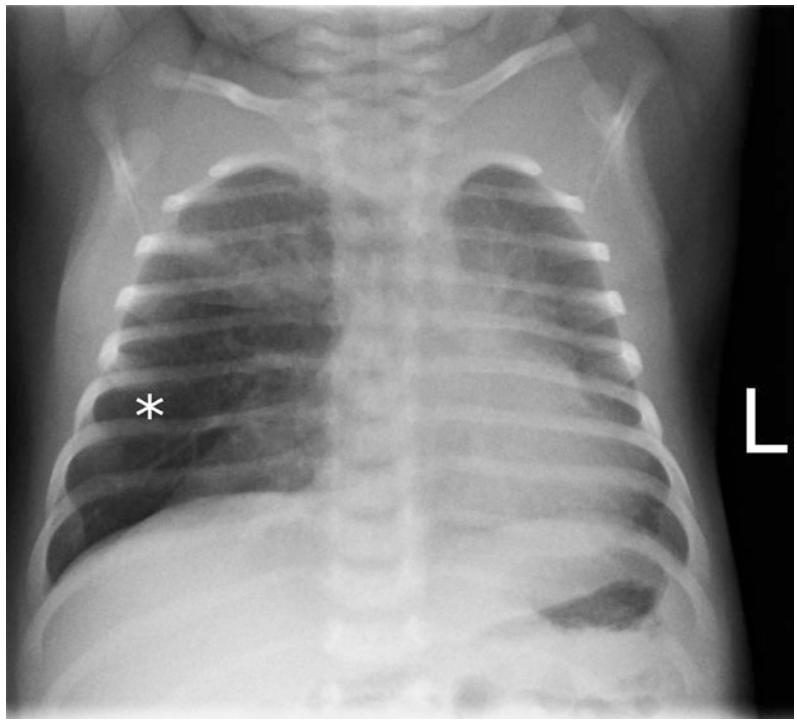

Fig. 1 Conventional chest X-ray in a patient with congenital lobar emphysema (*) in the right middle lobe with hypodense structure and mediastinal shift (with kind permission from the Department of Pediatric Radiology Klinikum Dortmund)

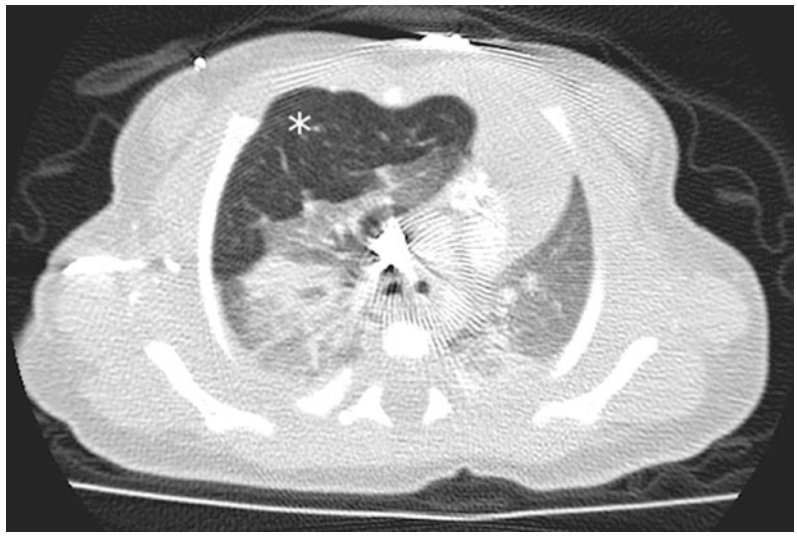

Fig. 2 Computed tomography scan in the same patient as in Fig. 1 with congenital lobar emphysema (*) in the right middle lobe, presenting as cystic tissue with less intensity and with mediastinal shift to left side by space consuming lesion (with kind permission from the Department of Pediatric Radiology Klinikum Dortmund)

Large lobar BA can mimic main-stem bronchial atresia with contralateral pulmonary hypoplasia, mediastinal shift and hydrops secondary to cardiac affection. While main-stem BA remains lethal, large lobar BA reduces its size by about 50% at a median gestational age of 32, 6 weeks [7, 8]. Bronchopulmonary foregut malformations lead to bronchogenic cyst (BC) typically found in the mediastinum, including the paratracheal, hilar and subcarinal space [2]. Atypical localizations have been described: e.g. intrapulmonal, intraoesophageal, intraspinal, intradiaphragmatic, intracardial, pericardial and even subdiaphragmatic [9–13]. The symptoms are caused by the affection of surrounding tissue and anatomic structures as well as signs of infection of the cyst or adjacent and affected tissue [14].

Bronchopulmonary Sequestration

There are two types of bronchopulmonary sequestration (BPS): intralobar and extralobar. BPS has an estimated overall prevalence of 1 in 1000 births. It is characterized by having its own blood supply, usually out of the systemic circulation, and not having a connection to the tracheobronchial tree [15]. This is due to the separation of a small part of the lung during its embryonal development out of the foregut [1]. Intralobar BPS are the most common form (75%) and surrounded by capable lung and a common pleura, having their own blood supply from a systemic vessel and draining to the pulmonary circulation [16]. One out of four BPS (25%) is extralobar and covered by a separate pleura visceralis, [15, 17]. The most typical location for these is the dorso-basal part of the left hemithorax between left lower lobe, diaphragm and esophagus (Figs. 3 and 10a) [18]. Afferent vessels originate most commonly (80%) from the thoracic or abdominal aorta, but care has to be taken because blood supply can derive from the subclavian artery, coronary artery or intercostal arteries (Figs. 7 and 8) [19, 20]. Efferent vessels drain either to systemic (azygos and hemiazygos vein, subclavian vein or portal vein) or pulmonary circulation (pulmonary vein) together with the afferent artery in a single vascular pedicle. When a bronchus is found in that pedicle, a communicating bronchopulmonary foregut malformation and connection to the esophagus might coexist [21]. Less than half of the patients, with either

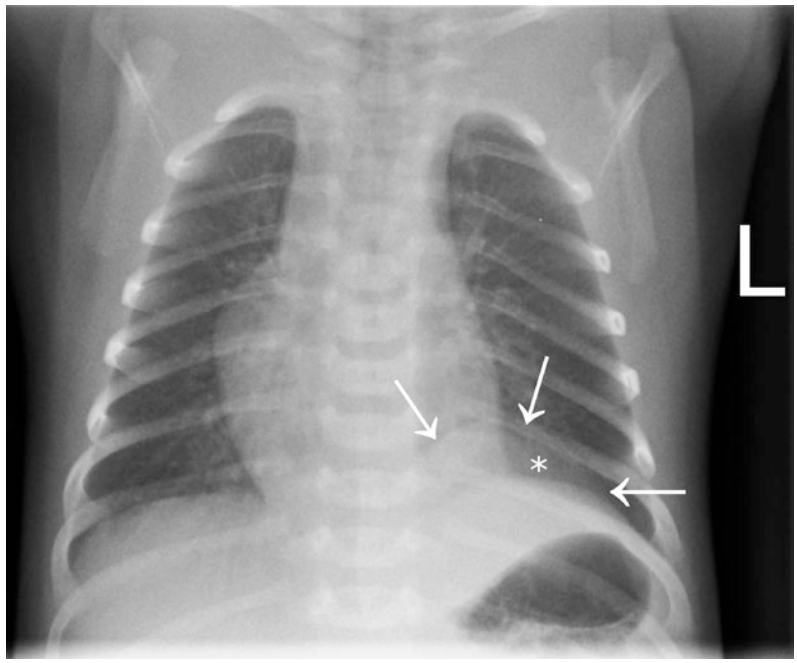

Fig. 3 Chest X-ray of an asymptomatic newborn with prenatally diagnosed extralobar BPS (*) in the lower left hemithorax. High density line (←) between sequester and air-filled lung (with kind permission from the Department of Pediatric Radiology Klinikum Dortmund)

intra- or extralobar BPS, show symptoms like dyspnea, cystic aberration and consecutive infection, artery-venous shunting and successive cardiac failure (in fetuses leading to hydrops) [22]. Extralobar BPS most often are found incidentally with associated congenital deformities (CPAM, diaphragmatic hernia, vertebral bodies deformities, heart failure, foregut duplication) [23].

Congenital Pulmonary Airway Malformations

CPAMs generally are connected to the tracheobronchial tree and the pulmonary vascular system. Histological findings are exaggerated growth of the terminal bronchioles and suppressed alveolar formation leading to solid and cystic benign malformation of the lung. Histologically five subtypes can be divided based on embryologic level of origin and their characteristics (Type 0 corresponding to the proximal bronchial anomaly and type IV corresponding to the peripheral lung anomaly) (Table 1) [24, 25]. Clinical graduation into microcystic or macrocystic lesions (size of cysts smaller or lager than 5 mm) as well as the CPAM volume ratio, the CVR (= product of widest length, width and depth multiplied by 0.52 and divided by the head circumference in cm = [L × W × D × 0, 52/HC]) is important for prognosis since microcystic lesions and those with a CVR ≥ 1.6 are associated with hydrops and high risk of pulmonary interference with respiratory distress [6, 26–28]. Macrocystic lesions are usually located in one single lobe of the lung (Figs. 4 and 5) [1]. The malignant pleuropulmonary blastoma (PPB) can mimic a CPAM, whereas a clearly preoperative distinction is not possible, thus histologic diagnosis should be acquired for these patients. However, if the relationship between CPAM and PPB is causal, correlational, or coincidental is still matter of debate [29]. The prevalence of CPAMs is approximately 1 in 7200 live births [30]. Congenital pulmonary airway malformations (CPAM) with aberrant blood supply are called hybrid lesions [31].

Table 1 Overview of congenital malformations of the lung. CPAM classification: Types I, II and IV are seen as macrocystic lesions, Type III as microcystic lesions. The latter is larger and has a poorer prognosis [24]

Congenital pulmonary airway malformation (CPAM)	Type 0	Small cysts
	Type I	Small number of large cysts (3–10 cm)
	Type II	Smaller cysts (0.5–2 cm) and solid areas; highest risk of synchronic organic malformations
	Type III	Very small cysts mimicking a solid and on ultrasound echogenic mass
	Type IV	Large cysts (10 cm)
Hybrid lesions		CPAM with aberrant blood supply
Bronchopulmonary sequestration (BPS)		Intralobar BPS with own blood supply from a systemic vessel, surrounded by normal lung, common pleura visceralis
		Extralobar BPS with own blood supply, usually out of the systemic circulation (often aorta), separate pleura visceralis
Congenital lobar emphysema (CLE)		Echogenic homogeny tumor, rarely diagnosed in prenatal US, not apparent until the first days of a new born
Bronchial atresiea (BA)		Obstruction enclosing the fluid produced by the lung
Bronchogenic cyst (BC)		Typically found in the mediastium

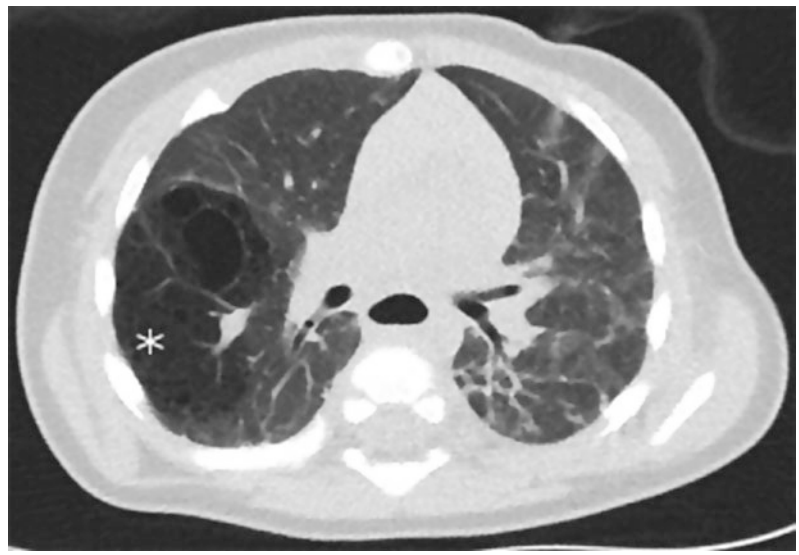

Fig. 4 CT scan with hypointense area (*) with multiple cysts of different size in the right lung expected to be a CPAM in the middle lobe—intraoperatively found in the apical segment of the right lower lobe (segment 6), histopathologically CPAM type II (with kind permission from the Department of Pediatric Radiology Klinikum Dortmund)

Diagnosis

Prenatal

Prenatally congenital malformations of the lung are most often found in ultrasound [US] examinations during pregnancy in the second trimester. US is an ubiquitary available and cheap technique generating reproducible high resolution images of echogenic masses, cysts, pleural effusions, hydrops or mediastinal shifting [2]. Abnormalities can be detected both intrathoracical and intraabdominal. Combined with B-Mode Doppler US can even provide

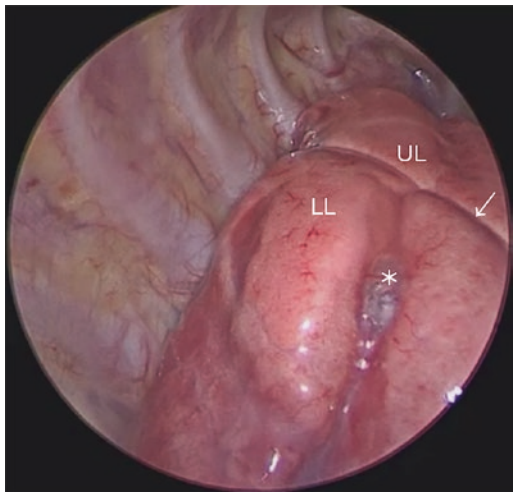

Fig. 5 (Same patient as in Fig. 4) Thoracocenteses in the 3rd ICR in right middle axillary line with insertion of a 3 mm diameter 30 degree optic camera: Intraoperative view from lateral on the surface of the right lung, the upper lobe (UL) on the top, the oblique fissure (←) is coming from the right and the lower lobe (LL) with the altered surface (*) marking the CPAM type II in segment 6 in the center of the image

more information concerning systemic or pulmonary feeding arteries and localization (intralobar or extralobar) when draining veins are identified [31]. Fetal echocardiography may show pulmonary hypertension due to lung hypoplasia as well as hydrops fetalis induced by compromising thoracic masses [27]. Magnetic resonance imaging (MRI) as additional imaging technique can help to define expected entity and size of the malformation. It can supply the counseling medical staff and parents-to-be with further information for planning prenatal treatment, process of delivery and postnatal procedure. MRI should be used to furthermore characterize the lesion and confirm diagnosis made by US or distinguish it from differential diagnosis such as diaphragmatic hernia, teratoma and other fetal masses [32, 33]. In the characterization of CPAMs MRI is limited due to its poor spacial resolution, though it can help to evaluate the CVR and thereby the prognosis [2, 28, 34]. These lesions should be image-controlled by US with short interval during 20th to 28th week of gestation, because pulmonary lesions grow fast during this period. Serial ultrasound is suggested weekly in CVR < 1.6 and twice weekly in CVR ≥ 1.6 and in dominant cysts until a growth plateau is seen [27]. In onward pregnancy somatic growth of the fetus exceeds growth of the lungs and thereby even large thoracic masses (especially CPAMs) can regress spontaneously and symptoms like hydrops may disappear. By becoming isoechogenic with the adjacent normal lung, lesions might seem to vanish in US at 32–34 weeks of gestation, though they are still verifiable in postnatal MRI or computed tomography (CT) scans [27].

Postnatal

Postnatal respiratory suspicious newborns undergo clinical examination. Heart auscultation focus may be displaced by mediastinal shift and altered ventilation sounds can occur [35]. A plain chest X-ray can give further information, despite macrocystic lesions filled with amniotic fluids don't have to be visible until some days later air has replaced the fluids. Microcystic lesions however remain unchanged. Even prenatally clearly examined malformations can come with a normal chest X-ray after birth [27]. X-ray is standard in diagnostic of CLEs (Fig. 1). BPS need to be examined by experienced US radiologists to gather further information about vascularization and localization (Figs. 6 and 7). In asymptomatic patients with CPAMs literature clearly recommends a CT scan, adding valuable information about the type, localization and (with vascular contrast-enhancement) vascular supply of the malformation (Fig. 8) [2]. CT scanning is the standard procedure for planning any kind of treatment, especially surgery. Timing of the CT basically depends on symptoms, X-ray findings and planed timing of resection [36]. However definitive diagnosis can only be made by histological examination after resection.

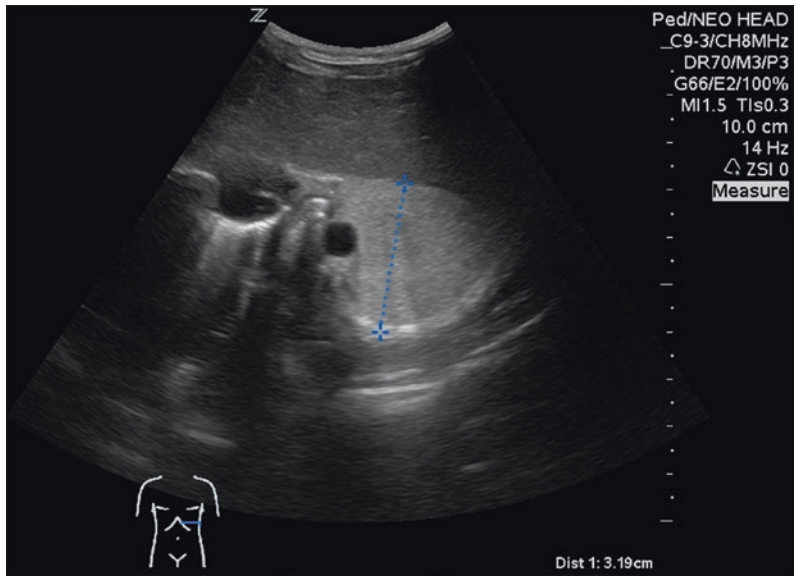

Fig. 6 Postnatal transversal B-mode ultrasound image of the same patient as in Fig. 3 with measurement of the BPS (blue spotted line, distance 3.19 cm) (with kind permission from the Department of Pediatric Radiology Klinikum Dortmund)

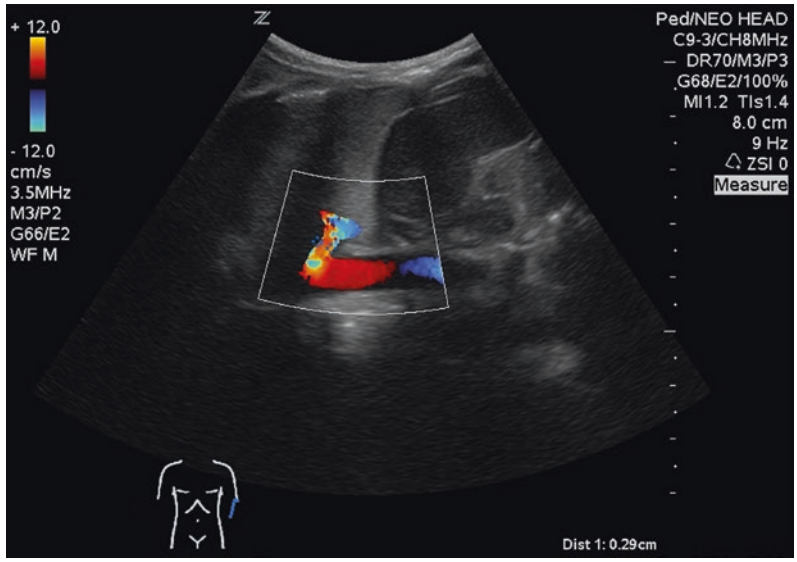

Fig. 7 Doppler ultrasound demonstrates the vascularization of the sequester, shown in Figs. 3 and 6. Afferent artery is originating from thoracic aorta (with kind permission from the Department of Pediatric Radiology Klinikum Dortmund)

Fig. 8 Post contrast coronal CT reconstruction in another patient with an extralobar BPS (*) in the left lower hemithorax, blood supply by an artery originating from the abdominal aorta (→) (with kind permission from the Department of Pediatric Radiology Klinikum Dortmund)

Indication of Treatment

Prenatal

The necessity of treatment depends on clinical symptoms and the potential for malignancy or the risk of malignant conversion of the lesion. Prenatal indication for treatment depends on size and character (cystic or solid) of the lesions and symptoms of the patients (hydrops and cardiac failure, mediastinal shift). In cystic malformations with a CVR $\geq$ 1.6 and severe mediastinal shift, hydrops or evolving heart failure a fetal intervention and surgery should be interdisciplinary discussed between surgeons, radiologists and obstetric gynecologists specialized in prenatal diagnostic [27]. If the malformation is solid (microcystic), previous maternal corticosteroids may induce an earlier growth plateau of the lesion and resolve mediastinal shifting and hydrops, thus delivery and elective postnatal resection can be achieved [37].

Postnatal

After birth resection of lesions is recommended before the onset of first symptoms [36]. But, because of an increased risk of anesthesia and a challenging operative treatment in neonates, newborns and babies, asymptomatic lesions should be observed for the first months of life. Patients with a CPAM without symptoms before or at birth, only have a small risk of becoming clinically symptomatic. The risks of an unclear distinction to pleuropulmonary blastoma (PPB), a malignant degeneration to bronchoalveolar carcinoma and rhabdomyosarcoma as well as the doubled operative risk (complications including air-leak, effusion, pneumonia and bleeding) if resection is performed after symptoms occurred, lead to the recommendation for elective surgery prior to 6–10 months of age [36, 38, 39]. An algorithm may help to categorize a lesion as CPAM: prenatal detection, afferent vessel derived of the systemic blood circulation, asymptomatic and hyperinflated lung. A factor that indicates a PPB is: bilateral or multisegmental involvement [40]. Treatment strategy for patients with asymptomatic CLE is primarily conservative. Cases presenting, either straightaway or during follow up, with severe symptoms, should undergo complete resection [64]. Asymptomatic BPS with little blood flow (shunt) often show total remission with time [41]. Symptomatic BPS with a high shunt volume and evidence of heart failure should undergo angiographic embolization or ligation of the vessels

followed by surgical resection. Cystic, especially intralobar BPS should be resected, likewise, prior to first infection, because of the risk for malignant conversion (carcinoid tumor) of BPS [17]. Size constant, extralobar BPS without cysts, located close to the diaphragm with identifiably systemic efferent vessels may be observed [17].

Therapy

Prenatal Care

Steroids are well described as most effective non-invasive therapy in prenatally diagnosed congenital malformations of the lung. Dexamethasone or betamethasone decrease effusions, potentially downsize the lesion and resolve hydrops [27]. Maternal betamethasone given intramuscularly should be considered as initial therapy in fetus with microcystic lesions and hydrops [36]. However, showing lower intrauterine death rates in retrospective studies, the effect of the increased somatic growth with proportional shrinking of the malformations mass in ongoing pregnancy remains unclear and prospective randomized trials are needed for further recommendations. Nevertheless, multiple courses of betamethasone should be applied in fetuses failing to respond to a single dose, considering that failure to respond can indicate necessity for fetal or early neonatal intervention [42].

Fetal Intervention

Until today no evidence for fetal intervention shows clear benefit of decompressive thoracocenteses, placement of thoracoamniotic shunt or open fetal surgery. By the lack of randomized studies and long-term follow-up reports, it remains unclear which patients may benefit from fetal intervention. Extensive multidisciplinary counseling of the parents-to-be about capability and risks of fetal therapy is mandatory. Expectantly management should be continued as long as cardiac function of the fetuses, measured by echocardiography, stays satisfactory. After the 28th week of gestation spontaneous regression is usual. In those patients without mediastinal shift, planed delivery and elective postnatal resection is recommended [37]. In fetuses below the 32nd week of gestational age with increasing size of a cystic lung lesion and complicated hydrops fetalis (with cardiac derogation) or significant mediastinal shifting in-utero, drainage of primary hydrothorax may improve perinatal survival [43]. Prior to the placement of a shunt, one or two fetal thoracocenteses with cell count, culture studies, karyotype/genetic analyses and observation of the cyst shrinking by drainage should be done [44]. Repetitive thoracocenteses (up to three) seem to be legitimate and should be seen as diagnostic procedure although spontaneous regression may be observed. If fluid reaccumulates rapidly thoracoamniotic shunt placement should be considered [45]. Both thoracocenteses and shunt placement is performed under continuous US guidance using a standard aseptic technique. By using a narrower shunt and needle, the associated risk of premature rupture of membranes or fetal injury (intercostal artery bleeding may lead to death) decreases while the risks for obstruction, migration and need for re-shunt-placement is higher. Perioperative medication with tocolytics and antibiotics and frequent US re-evaluations are recommended [46]. Fetal or infant death rates are high (up to 30%) and short interval from fetal intervention to delivery is reported [37]. Contraindications are early gestational week (<16), coexisting chromosomal and major fetal abnormalities as well as maternal infections (risk of fetal transmission) [45]. Symptomatic microcystic lesions require fetal treatment for the same reasons as cystic ones. If steroid treatment fails, they need resection of the affected lobe as they do not shrink by fluid decompression. Currently, one single case of successful open fetal surgery in the 25th week of gestation in mainsteam and lobar bronchus atresia is reported in the current literature [47]. Lower transverse abdominal incision, hysterotomy and surgery on the fetus under deep maternal-fetal

general anesthesia and fetal peripheral venous supply of anesthetics, analgesics and volume (usually fresh, warm blood) are made [48]. US guidance helps locating the side of the lesion and lobectomy by thoracotomy is followed by restocking of the amniotic fluid and closure of uterus and abdominal wall. Continuous and close US and echocardiography examinations are indicated to monitor resolving of hydrops and growth of the surrounding, capable lung until delivery by cesarean section is performed as close as reasonable to term [49]. Because of high mortality and morbidity after fetal intervention in contrast to the usually good prognosis and excellent postnatal therapeutic options, the indication for fetal surgery should be well and restrictively discussed.

Perinatal Surgery

Ex-utero-intrapartum-treatment (EXIT) was first described in 1996. Initially, this method was developed for removal of tracheal balloons, placed interventional in fetuses with congenital diaphragmatic hernias [50]. Fetuses with severe lesions without the necessity for primary fetal intervention undergo clinical observation or therapy with steroids. Those with a large thoracic mass (CVR > 2) and / or persistent mediastinal shifting, that is expected to compromise respiratory or cardiac function immediately after birth, may in some cases benefit from EXIT-to-resection procedure. Partial delivery of fetal head, neck and chest through a stapled hysterotomy maintaining placental support is performed under maternal inhalational anesthetics and supplemental analgesics. Peripheral venous catheter and pulse oximeter is placed on the fetal upper extremity and intubation without ventilating is done to preserve fetal and placental circulation and to avoid expansion of the lesion that would aggravate heart and lung function. After posterolateral thoracotomy and exteriorization of the mass ventilation is attempted, and in the case of adequate gas exchange, the operation is continued after complete delivery and transfer to another operating room. In the case of inefficient gas exchange, fetuses can be treated under placental support or extracorporeal membrane oxygenation (ECMO) [48, 50, 51].

Postnatal Surgery

Congenital malformations of the lung in asymptomatic patients should be resected electively 6–10 months after birth [36]. In symptomatic patients earlier and even urgent treatment may be necessary. A team of pediatric surgeons with thoracic surgical skills and experienced pediatric anesthetists realize a feasible and safe therapy with minimal morbidity by resection. Surgical treatment should be planed on preoperative CT-based information (Figs. 4 and 8). Localization and size as well as expected entity influence operative modalities regarding operation technique (video-assisted thoracoscopic surgery = VATS versus conventional open surgery = COS) and dimension and radicality of resection (lobectomy, segmental resection, non-anatomic resection and as an ultima ratio procedure pneumonectomy). Primary goal is complete resection of the lesion. Standard for most patients is lobectomy [27]. Other lung-sparing resections (LSR) have been described as safe and feasible but seem to be accompanied with increased rates of residual disease (up to 15% in CPAM) [39]. In older studies a longer period of postoperative air leak and chest tube duration after sublobar resections have been reported, while improved modern technical tools for tissue sealing nowadays supersede this disadvantage [52]. No clear benefit in patients with LSR compared to lobectomy regarding perioperative morbidity or long-term pulmonary function is shown currently. Overinflating of the remaining lung and subsequent alveolar multiplication compensates vital capacity in children undergoing surgery younger than 5 years of age [53]. In very few patients with extensive multilobar involvement, pneumonectomy seems to be necessary. Whenever reasonable in these cases, non-anatomic resection even with small residual normal lung can avoid the post-pneumonectomy syndrome with shifting of the mediastinum and symptomatic central airway compression [54]. In contrast to the dimension of

resection, the operation technique effects the long-term pulmonary function (VATS better than COS) [55]. Although VATS is associated with longer operation time it comes along with a significant lower short-term perioperative complication rate, less midterm musculoskeletal sequelae and a better cosmetic outcome—as it is well known and has been previously described in adult thoracic surgery [56–59].

Operative Management

Due to the lack of small endotracheal double-lumen tubes for single lung ventilation in infants, contralateral lung ventilation by selective mainstem intubation, with an uncuffed tube, one half to one size smaller than in standard intubations, is usual. Overflow ventilation caused by the uncuffed tube is counteracted in VATS with low flow (1 L/min) and low pressure (4 mmHg) CO_2 infusion during the thoracoscopy. COS is usually performed by postero-lateral or muscle-sparing antero-lateral thoracotomy in lateral decubitus position. An anterior approach during VATS helps to keep the surgeon, the camera, the pathologic mass and the monitor in one line (Fig. 9) [58]. The camera trocar should be positioned in the 5th or 6th intercostal space between and above the working ports to allow a view on relevant structures similar to the view in COS (Fig. 10a). If a circumscribed area is point of interest, ports can

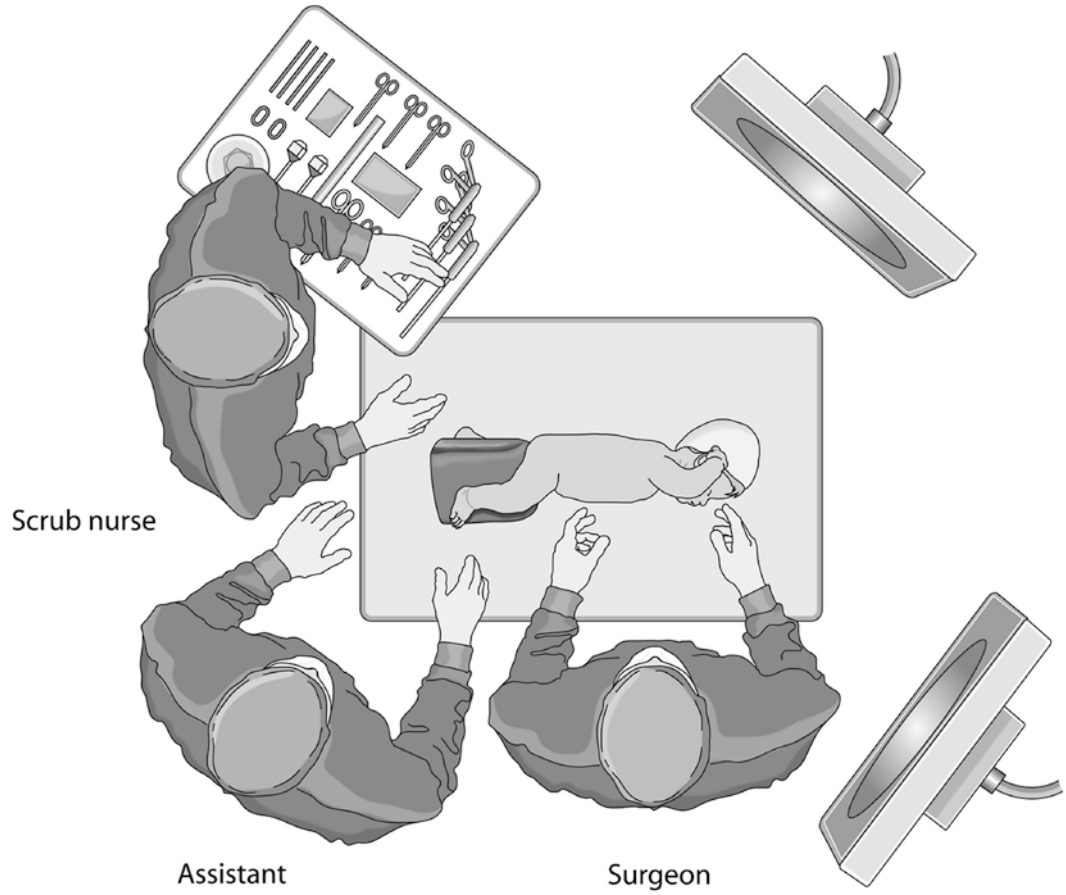

Fig. 9 Patient in lateral decubitus position. Anterior approach. The assistant standing on the same side of the table as the surgeon, thus no inversely working on the camera complicates handling (*Source* From Rothenberg, Steven S. (2008): Thoracoscopy in Infants and Children: Basic Techniques. In: N. M. A. Bax (Hg.): Endoscopic surgery in infants and children. Berlin, New York: Springer, S. 89–94, with permission from Springer)

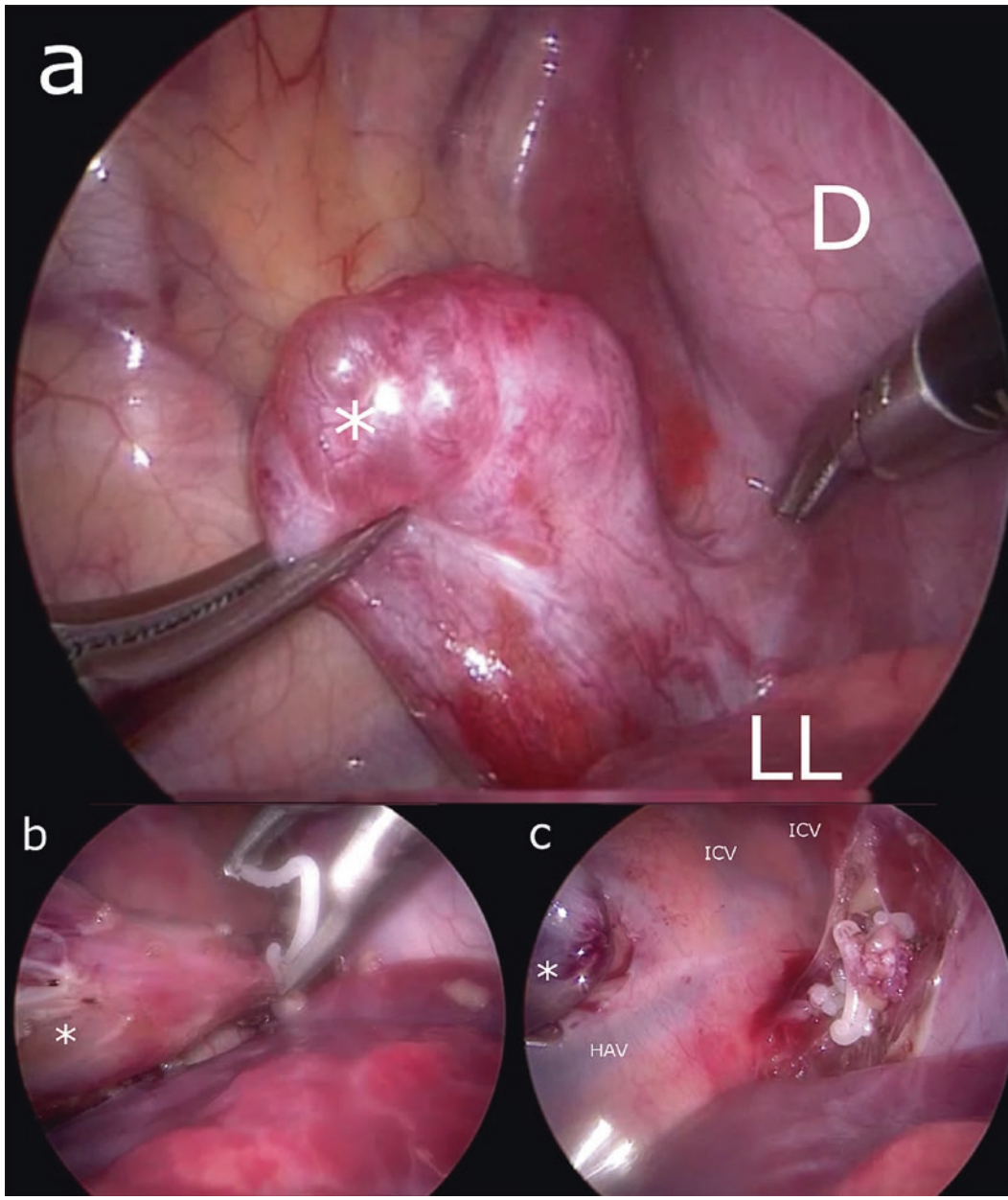

Fig. 10 Video-assisted Thoracoscopy in a patient with an extralobar BPS in the left lower hemithorax. View from the thoracocentesis placed in 5th ICR in middle axillary line with a 5 mm diameter 30 degree optic camera down in the dorsomedial costodiaphragmatic recess: **a** intraoperative view on a sequester (*) located in the lower left Hemithorax between lower lobe (LL) and diaphragm (D) with blood supply from the abdominal aorta, **b** the sequester (*) being tired aside, placing three clips after preparation of the vessels, **c** view on the clipped vessels, hemiazygos vein (HAV) and the intercostal veins (ICV); the sequester (*) can be removed with an endobag

be placed in a triangular arrangement, using the localization of the lesion as focal point of the triangle to allow best view on this spot. Especially in children, the lowest intercostal spaces are the widest and larger ports need to be placed the lowest as possible. Usually a three port

technique with 3–5 mm instruments is performed. Endoloops (pre-tied ligatures), endoscopic staplers and clips as well as energy devices such as monopolar or bipolar cautery, ultrasonic coagulating shears and other ultrasonic devices enable the surgeon to seal lung tissue, including even main pulmonary vessels (Fig. 10b, c). A widened port site allows to remove the resected specimen, if possible being intact for further pathologic evaluation. If placement of a chest tube for drainage is necessary, it can usually be removed within 1–2 postoperative days. In children with BPS causing cardiac decompensation, due to high blood shunt volume, embolization of the afferent vessels, either as the definitive therapy or prior to surgical resection, is feasible and sufficient [60]. Intraabdominal BPS should be resected electively by laparoscopy or laparotomy, not effecting the pulmonary parenchyma [27]. After discharge all patients should be monitored in long-term follow-up for lung and cardiac function, compensatory lung growth, chest wall deformities and recurrence.

Summary

Congenital malformations of the lung result in a closure or atresia of the connection to the tracheobronchial tree, a topical embryonal maldevelopment of lung tissue, a vascular malformation or extraanatomical vascularization. Lesions, that are usually incidentally found in prenatal period, need serial ultrasound within a short interval and fetal echocardiography until week 28 of gestation to monitor, if pulmonary hypertension or hydrops fetalis appear. In the third trimester of gestation even large thoracic masses can regress spontaneously. Regarding the risks of unclear distinction and malignant degeneration, elective resection is recommended. Computed-tomography scan and operation should be performed at 6–10 months of age in asymptomatic patients, preferably prior to first symptoms. Lobectomy by video-assisted thoracoscopic surgery is a safe and sufficient procedure for most congenital malformations of the lung. Due to compensatory lung growth no loss of pulmonary function needs to be expected in children younger than 5 years of age at time of operation.

Self-study

1. Lung sparing resection in patients with congenital malformations of the lung is:
   a. Segmentectomy and pneumonectomy.
   b. Connected with shorter period of chest tube.
   c. Followed by increased rates of residual diseases.
   d. Always better for postoperative long-term pulmonary function.
2. VATS in comparison to COS in patients with congenital malformations of the lung is:
   a. Associated with a lower complication rate.
   b. Leading to more musculoskeletal sequelae.
   c. Not feasible in children under 10 kg.
   d. Not safe in terms of air- and blood tight sealing.

Answers

1. Lung sparing resection in patients with congenital malformations of the lung is:
   a. Segmental resection, non-anatomic resection.
   b. Used to be connected with longer period of air leak and chest tube.
   c. Followed by increased rates of residual diseases—CORRECT.
   d. No clear benefit in patients with LSR is shown.
2. VATS in comparison to COS in patients with congenital malformations of the lung is:
   a. Associated with a lower complication rate—CORRECT.
   b. Leading to less musculoskeletal sequelae and a better cosmetic outcome.
   c. Safe to perform in even very young children.
   d. Modern endoscopic instruments (staplers, energy sources, ultrasonic shears and others) provide safe tools for endoscopic tissue sealing [61–63].

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The Right Lung

Camilla Poggi, Claudio Andreetti, Cecilia Menna, and Mohsen Ibrahim

Key Points

1. The anatomic subunit of the lung is the bronchopulmonary segment, with its own pulmonary arterial supply, pulmonary vein drainage and its own bronchus ventilation.
2. Intimate knowledge of the anatomy of the fissures, the recess of the pericardium and the relationships between the lobes and the vascular structures of the mediastinum allow complete control of the structures despite the surgical complexity.
3. A deep understanding of the surgical anatomy of the right lung is mandatory to perform a right pulmonary resection and reconstruction as well as lung transplants.

Surgical Anatomy

Introduction

To perform anatomical pulmonary resection and reconstruction and lung transplant a deep knowledge of the surgical anatomy is mandatory. Hereby, we report a synthesis of the core aspects of the surgical anatomy of the right lung.

The right lung is the larger of the two lungs and is divided in three lobes: the upper, middle and lower lobes. In the right lung we can find two fissures: the major and minor fissures. The major fissure separates the upper and middle lobes from the lower lobe. It runs diagonally from the superior to the inferior lateral surface of the lung; it begins posteriorly at the level of the 5th intercostal space, running downward the course of the 6th rib and ending at the diaphragm at the level of the 6th costocondral junction. On the other hand, the minor fissure separates the upper lobe from the middle one; it is usually less evident. It runs horizontally in the upper portion of the lung beginning in the major fissure in the region of the midaxillary line at the level of the 6th rib and running anteriorly to the costochondral junction of the 4th rib [1].

The right lung is fixed centrally by the hilum that is composed by the right main bronchus, the pulmonary artery and the superior and inferior pulmonary veins, and distally by the inferior pulmonary ligament, that is the reflection of the inferior mediastinal parietal pleura onto the lung and it usually envelop the inferior pulmonary vein.

The bronchopulmonary segments can be considered as an independent lung unit with its own pulmonary arterial supply, pulmonary vein drainage and its own bronchus ventilation

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[2]. The right lung is composed by ten segments; three are usually present in the upper lobe (apical, posterior and anterior), two in the middle lobe (lateral and medial) while five are located in the lower lobe (superior, medial basal, anterior basal, lateral basal and posterior basal) (Fig. 1).

Lobation anomalies cannot often be found; this condition usually results from too many or too little fissures. Accessory fissures are

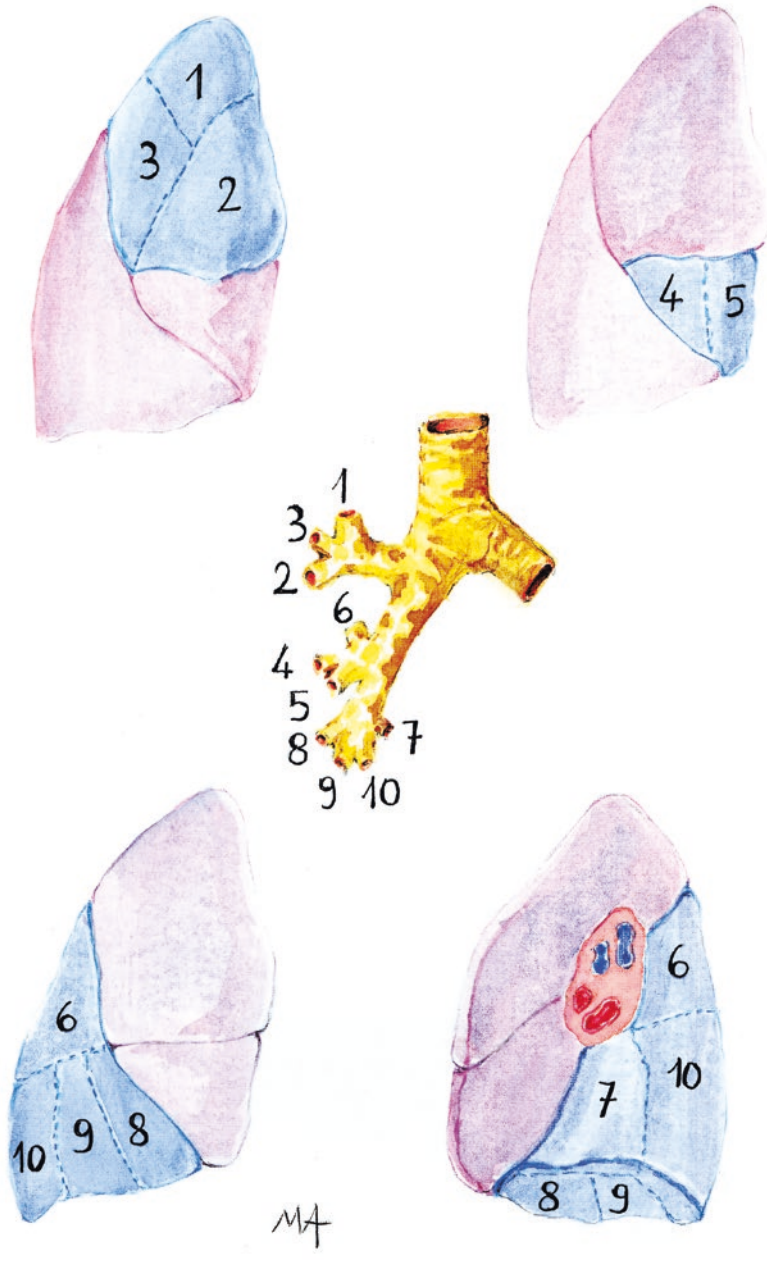

Fig. 1 Lobes and segments of the right lung. Right upper lobe segments: 1 apical; 2 anterior; 3 posterior. Middle lobe segments: 4 lateral; 5 medial. Right lower lobe segments: 6 superior; 7 medial basal; 8 anterior basal; 9 lateral basal; 10 posterior basal

normally located on the planes of division of bronchopulmonary segments and their presence is estimated due to the presence of an accessory lobe. A bronchial communication between a certain lobe and the main airway is infrequently present, as it is in the case of the tracheal lobe, where the lobe is the apical segment of the upper lobe with a tracheal origin of the bronchus. When no bronchial communication exists, the accessory lobe can be considered as the real extralobar sequestration. Fusion of adjacent lobes can be found when a fissure is incomplete or is totally absent. The most common variation is a complete fusion of the middle lobe and the anterior portion of the upper lobe, which is seen in more than 50% of the examined lungs.

Right Pulmonary Artery

The right main pulmonary artery arises from the main pulmonary artery when it passes below the aortic arch. The direction of the pulmonary artery on that side is diagonal, passing posteriorly to the aorta and the superior vena cava. In this portion it is included in the pericardial sac and it is covered, for more than three fourths of its length and circumference, by serous pericardium, but its posterior surface beard down on the fibrous pericardium. At that point retracting the superior vena cava laterally and the aorta medially, the main pulmonary artery can be safely controlled and mobilized, allowing to the posterior fibrous pericardium. Here the division of posterior fibrous pericardium provides a trans-pericardial access to the trachea and to the main bronchi. The pulmonary artery exits from the pericardial sac when it passes behind the superior vena cava entering the hilum; at that place we can find, with the exception of 5% of patients, the postcaval recess of Allison that is bounded by the pericardial sac laterally, by the superior vena cava medially and by superior pulmonary vein inferiorly [3].

Entering the hilum, the pulmonary artery lies anterior and inferior to the bronchus; before the pulmonary artery enters the lung, its first branch originates: the truncus anterior branch [4]. The truncus anterior branch usually bifurcates in two branches (superior and ventral branches), rarely in three, and in 10% of patients it is the only arterial supply to the upper lobe. It usually supplies to apical and ventral segments of the upper lobe. In 90% of patients another branch arises from the mediastinal artery within the pulmonary parenchyma: the ascending branch. The ascending branch arises from the lateral and posterior aspect of the mediastinal pulmonary artery opposite to the middle lobe branch and usually supplies to posterior segment of the upper lobe (Fig. 2).

The middle lobe pulmonary artery is the first branch arising from the mediastinal pulmonary artery, after the truncus anterior branch of the upper lobe (Fig. 3). It originates from the anterior and medial surface of the mediastinal pulmonary artery at the same level of the ascending branch, usually at the level of the junction of the major and minor fissures. The arterial supply of the middle lobe is provided by a single artery in 46.5% of patients and by two arteries in 51.5%. The second artery arises more distally in 48.5% of patients, at the level of and opposite to the branch to the superior segment of the lower lobe; in 2.5% of patients it arises from a common trunk with a basal segmental artery and in 0.5% of patients it arises from the ascending branch of the upper lobe [5].

The mediastinal artery continues in its intraparenchymal portion downward the lower lobe, becoming the common basal pulmonary artery. The first branch that originates from that vessel is the superior segment of the arterial branch (Fig. 4). It's a single branch in 78% of patients, two branches in 21% and rarely is the arterial supply given by three branches. Superior segmental branches can arise as a common trunk either from the ascending branch of the upper lobe or from the basal segmental artery. The basal segmental artery usually lies posterolateral to the bronchus, it normally sends branches to the anterior basal and medial basal segments and ends by division into the lateral basal and posterior basal segmental arteries [5].

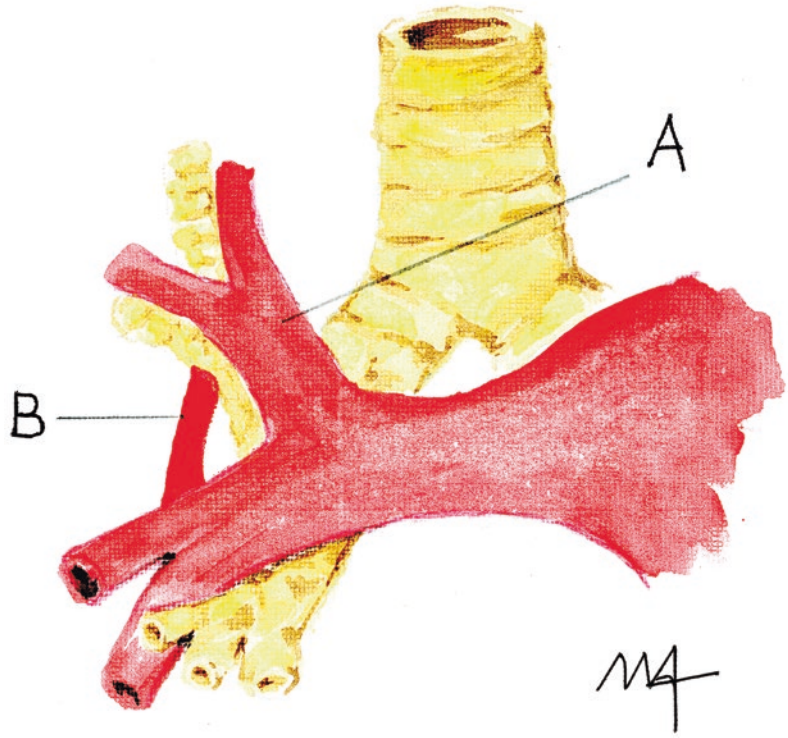

Fig. 2 Pulmonary artery of the upper lobe. A truncus anterior; B Posterior ascending branch

Right Pulmonary Veins

Right pulmonary veins are of two types: the superior and the inferior pulmonary veins. The superior pulmonary vein receives four branches: the first three branches drain the upper lobe while the forth drains the middle lobe; it lies anterior and partly inferior to the pulmonary artery. The three branches of the upper lobe are from above downward the apical anterior vein, the inferior vein and the posterior vein [6]. The inferior trunk of the superior pulmonary vein drains the middle lobe. The middle lobe vein is usually composed of two branches and ordinarily merges to the superior pulmonary vein before entering the atrium, occasionally it enters the pericardium and drains separately into the atrium or in some rare cases, it joins the inferior pulmonary vein before reaching the left atrium [7].

The inferior pulmonary vein lies posterior and inferior to the superior pulmonary vein; it usually drains the lower lobe and comprises two tributaries: the superior and the common basal branches. The first one drains the superior segment of the lower lobe whilst the second one, which is usually made up of superior basal and inferior basal branches, drains the basal segment of the lower lobe.

Unfrequently, more often in the right lung, a unilateral single pulmonary vein can be found. This condition is characterized by the joint of the superior and inferior pulmonary vein within the lung parenchyma or in the fissure forming a single trunk that drains the entire lung venous blood into the atrium. This rare condition is usually asymptomatic, but it may have serious surgical implications if not recognized during an anatomic lung resection [8].

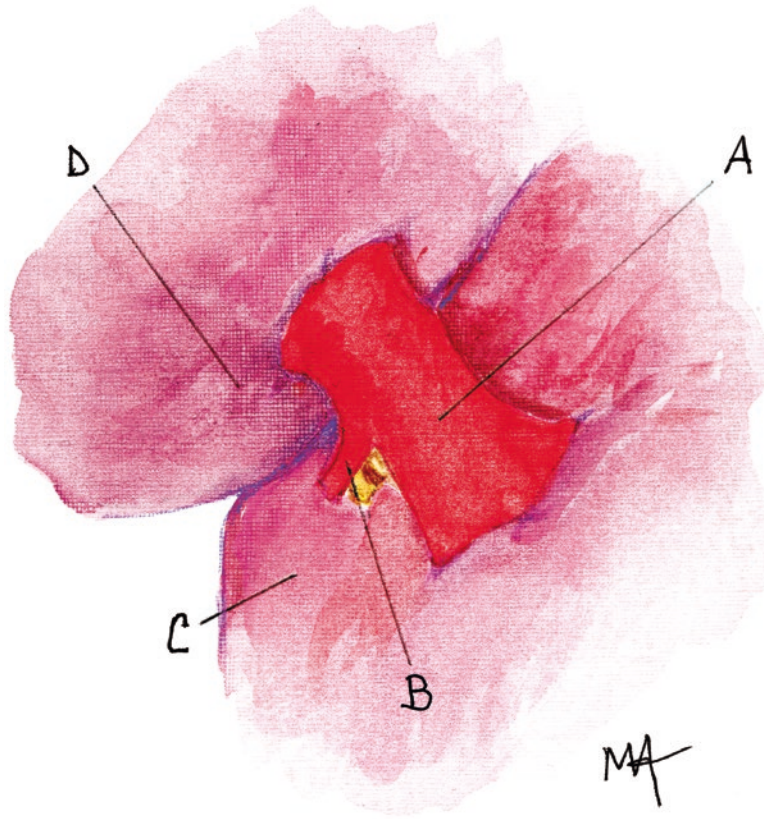

Fig. 3 Pulmonary artery of the middle lobe. A common basal pulmonary artery; B superior segmental pulmonary artery; C truncus anterior; D middle lobe pulmonary artery

Right Bronchial System

The right main bronchus is the most superior and posterior structure of the right hilum; it exits the mediastinum below the azygos vein (Fig. 5). The best way to appreciate the bronchial anatomy is through a bronchoscopy. The right main bronchus starts from the trachea at the level of the carina and ends at the level of the upper lobe bronchus takeoff; it is of 1.2 cm long, usually shorter and less angled compared to the left one. The upper lobe bronchus arises from the lateral wall of the main right bronchus, it is usually 1 cm long or less, and it separates in three segmental bronchi: the apical, the posterior and the anterior segmental bronchus. In 1.1% of patients a real upper lobe bronchus is not present and an immediate division into the segmental bronchi is seen [9]. Sometimes, it is possible to observe divergent combinations of these three major branches that might further subdivide to supply the various portions of the segments. The most common anomaly of the upper lobe bronchus is when the apical segmental bronchus arises directly and separates from other segments, into the main right bronchus or 2 cm above or at the level of the tracheal carina (tracheal bronchus) [10].

From the upper lobe bronchus takeoff, the bronchus intermedius starts and its length varies from 2 to 4 cm. It terminates at the origin of the middle and lower lobe bronchi. The middle lobe bronchus arises from the anterior surface of the bronchus intermedius. It is usually 1.2–2.2 cm long and bifurcates into a medial branch and a lateral branch; in 3% of patients an immediate bifurcated bronchus can be found.

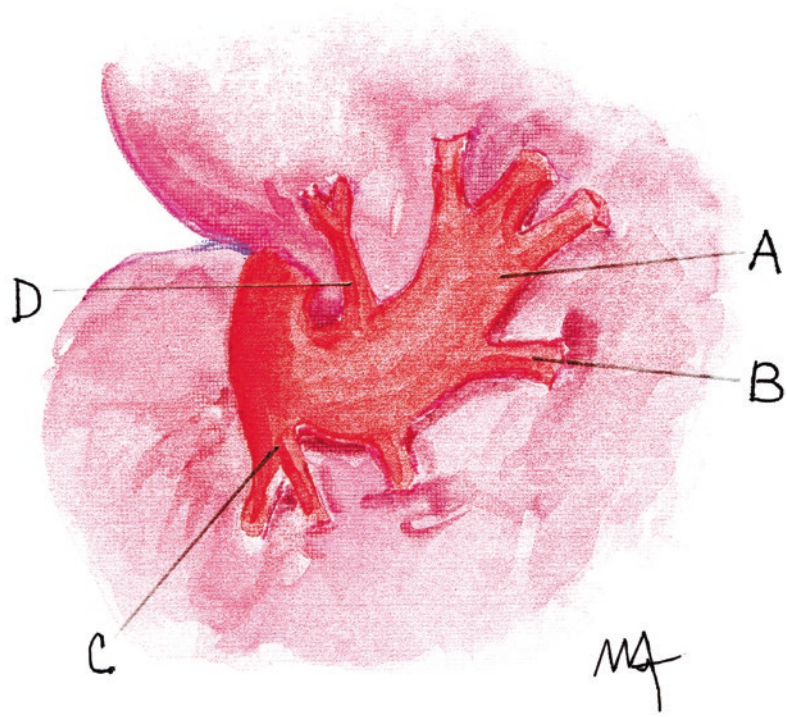

Fig. 4 Pulmonary artery of the lower lobe. A Common basal pulmonary artery; B right segmental pulmonary artery; C superior segment of the lower lobe; D right upper lobe

At the termination of bronchus intermedius the segmental bronchi of the lower lobe originates. A little distal to the middle lobe bronchus, on the posterior-lateral wall of the bronchus intermedius, the superior segmental bronchus of the lower lobe arises. This bronchus usually arises as a single branch and it normally divides itself in two or three branches; in 6% of patients it originates as two separate orifices [11]. Distal to the superior segmental bronchus are usually located the four basal segmental bronchi of the lower lobe. The most anteromedially bronchus is the medial basal bronchus that is tributary to the anterior and paravertebral surfaces of the lower lobe. Next to it there is the anterior basal bronchus arising on the antero-lateral aspect of the basal trunk and that usually splits in two major subdivisions. After this the lateral and posterior basal segmental bronchi can be found, they often originate as a common stem and each divides in two branches. During a right lower lobectomy, it is very important to identify the basal segmental bronchi and the superior segmental bronchus; sure enough when the distance with the middle lobe bronchus is limited, the taken in mass of the bronchus intermedius can compromise the middle lobe bronchus.

When a fissure is present between the parenchyma of the medial basal segment and other basal segments, this portion is called inferior accessory lobe. Similarly, the posterior accessory lobe can be seen when a fissure is present between superior segment and other basal segment.

The bronchial arterial system arises from the systemic circulation; the origins of the arteries are variable from the intercostal arteries, the aorta and rarely from the subclavian, innominate, internal mammary arteries and even from a coronary artery. The right bronchial arteries arise from the anterolateral or lateral surface of the aorta and rarely from the posterior wall,

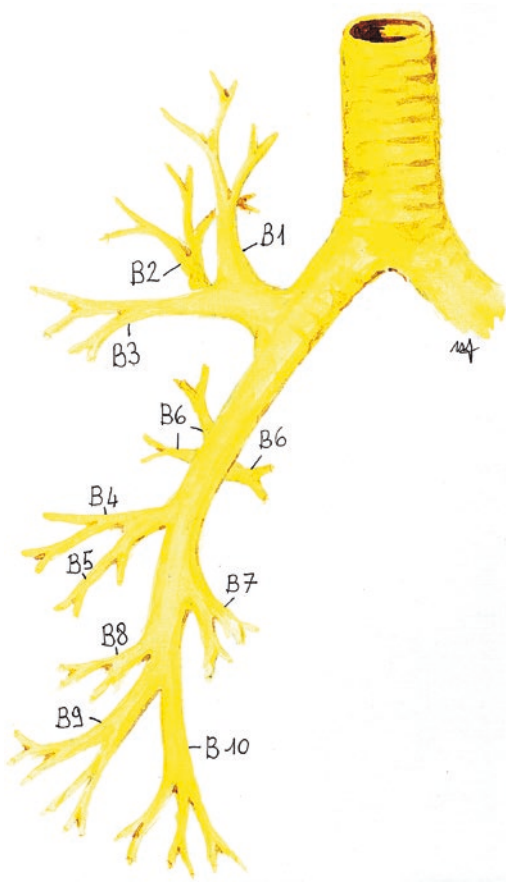

Fig. 5 Right bronchial tree. Upper lobe bronchi: B1 apical; B2 posterior; B3 anterior. Middle lobe bronchi: B4 lateral; B5 medial. Lower lobe bronchi: B6 superior; B7 medial basal; B8 anterior basal; B9 lateral basal; B10 posterior basal

usually between the levels of the 3rd to the 8th vertebral bodies. In the most part of specimens, analyzed by Caudwell and colleagues [12], the right bronchial artery arises in common with an aortic intercostal vessel, mostly from the first one. The arteries form a communicating arc around the main bronchus and from here they follow the course of the bronchus that divides as the bronchi do. The vessels are closely applied to the bronchial wall and the networks of intercommunicating vessels are usually present on it. Two-thirds of this blood supply empties into the pulmonary veins and the rest goes into the bronchial veins. The bronchial veins are both either present in the mucosa or external to the bronchial cartilage. The bronchial venous drainage directs the flow to the venous plexus of the perihilar region and afterwards into the azygos system [13].

Right Pulmonary Lymphatic Drainage

The lymphatic drainage pathway of the right lung comes from subpleural lymphatic vessels along lymphatic channels that are associated with the pulmonary veins to reach larger channels that run with the arteries and bronchi and subsequently into the segmental, lobar, interlobar, hilar and mediastinal nodes [14]. The parenchyma lymphatic channel drains into mediastinal lymph nodes generally ipsilaterally. It is possible to find anomalies of the lymphatic drainage, most frequently on the left side.

The right side pulmonary lymph nodes are divided into the intrapulmonary and bronchopulmonary nodes; the latter are subdivided into the lobar and hilar lymph nodes, varying in number and in location within the lung. Pursuing the first mapping system proposed by Naruke and colleagues [15], the regional lymph nodes are divided into 14 lymph node stations. The new lymph nodes map proposed by the International Association for Study of Lung Cancer (IALSC) [16] tries to conciliate previously proposed maps (Fig. 6).

From lymph node 1 to 9 they are considered mediastinal lymph nodes and from 10 to 14 they are intrapulmonary lymph nodes. Following the TNM classification [17], if a metastatic disease is present into the intrapulmonary lymph nodes, then patients are considered to have N1 disease; if metastases are present in ipsilateral mediastinal lymph node N2 disease and, if contralateral or supraclavicular metastases are present N3 disease.

The subsegmental nodes (station 14) are found adjacent to the subsegmental bronchi. The segmental lymph nodes (station 13) are usually related to the bifurcation of the segmental bronchi, and may be associated with pulmonary arteries; they extend out to the 5th or 6th order segmental bronchi. The lobar lymph node

Fig. 6 Regional lymph node stations: anterior (on the left) and mediastinal (on the right) view. Superior mediastinal nodes are station 1, 2, 3 and 4; aortic nodes are stations 5 and 6; and inferior mediastinal nodes are station 7, 8 and 9. Intrapleural nodes are stations 10, 11, 12, 13 and 14

(station 12) can be found at the angles formed by the origins of the different lobar bronchi and it lies nearby to the bronchus or beside the pulmonary artery; in the right lung they are most represented between the upper lobe bronchus and the middle lobe bronchus and in the region just below this latter [18]. A lobar lymph node is often found at the upper posterior end of the major fissure in the angle between the right upper lobe bronchus and the bronchus intermedius [19]. Constant lymph node can be found on the interlobar portion of the pulmonary artery, where the posterior ascending segmental branch of the upper lobe and the superior segmental branch of the lower lobe arise. Frequently the lobar lymph nodes are seen lying anteriorly among the upper lobe branches of the superior pulmonary vein.

The hilar lymph nodes (station 10) lie superior to the right main bronchus and classically have been considered to extend up to the inferior border of the azygos vein; they are in contact distally to the lobar lymph nodes and proximally to the mediastinal lymph nodes. The boundary between the hilar and the mediastinal lymph nodes is however blurred. Usually the lymph nodes medial to the main bronchus might be considered as hilar nodes when located departed from the tracheal carina and within the visceral pleura sheath, but as they start bordering to this structure they are best termed as mediastinal lymph nodes. In fact, determining whether these nodes are hilar or mediastinal nodes is a relevant oncological question that changes the staging and the subsequent patients' treatment [14, 20].

The mediastinal lymph nodes are located in the mediastinal compartment. The supraclavicular and sternal notch lymph nodes are considered as station 1, from the lower margin of cricoid cartilage to the clavicles bilaterally and in the midline the upper border of the sternal manubrium.

Upper paratracheal lymph nodes are considered as station 2. Station 2R goes from the apex of the right lung and pleural space to the intersection of the caudal margin of the innominate vein with the trachea, including lymph nodes extending to the left lateral border of the trachea. Thus, a last consideration is that it will be valid for station 4 too, this being due to the finding that the lymphatic drainage in the superior mediastinum predominantly occurs to the right paratracheal area and extends itself past the midline of the trachea.

Prevascular and retrotracheal nodes are known as station 3. Station 3a (prevascular) on the right side extend from the apex of the chest to the carina, considering as anterior border the posterior aspect of the sternum and as posterior border the anterior surface of the superior vena cava. Station 3b represents the retrotracheal nodes from the apex of chest to the carina.

Lower paratracheal nodes are considered as station 4. They are located in the obtuse angle between the trachea and the mainstem bronchus. On the right side they lay anterolaterally to the trachea and to the right innominate vein; they extend from the intersection of the caudal margin of the innominate vein with the trachea to the lower border of the azygos vein. This group includes right paratracheal nodes and pretracheal nodes extending to the left lateral border of the trachea.

The subaortic nodes (Aortopulmonary window) are considered as station 5 and paraortic nodes (Ascending Aorta or Phrenic) as station 6 and both are located on the left side of the chest and are discussed elsewhere in this book.

Subcarinal nodes are known as station 7 and they extend from the tracheal carina to the lower border of the bronchus intermedius. They are also known as inferior tracheobronchial nodes and lie in angle of the bifurcation of the trachea. Some of the subcarinal lymph nodes lie more posteriorly in relationship to the tracheal bifurcation; they are on the anterior surface of the esophagus and are so connected with the posterior group of lymph nodes.

The posterior mediastinal lymph nodes may be separate into two groups; the paraesophageal nodes and the nodes that are located either in the pulmonary ligament. The paraesophageal nodes (Below Carina) are considered as station 8, they are adjacent to the wall of the esophagus and to the right of the midline, extending from the lower border of the bronchus intermedius to the diaphragm. The pulmonary ligament nodes are known as station 9, they lie within the pulmonary ligament; they are usually two or more small lymph nodes. Close to the inferior border of the inferior pulmonary vein, it is usually possible to find the biggest pulmonary ligament node, which is often called the sentinel node of the pulmonary ligament [14, 20].

Self-study

1. The bronchopulmonary segments can be considered as:
   a. An independent lung unit with its own pulmonary arterial supply, pulmonary vein drainage and its own bronchus ventilation.
   b. An independent lung unit with only bronchus ventilation.
   c. An independent lung unit with its own pulmonary arterial supply and pulmonary vein drainage.
2. The middle lobe pulmonary artery:
   a. Is the last branch arising from the mediastinal pulmonary artery.
   b. Is the first branch arising from the main pulmonary artery.
   c. Is the first branch arising from the mediastinal pulmonary artery.
3. Find the correct sentence:
   a. The right side pulmonary lymph nodes are divided into the intrapulmonary and bronchopulmonary nodes: the first one are subdivided into the lobar and hilar lymph nodes.
   b. From lymph node 1 to 9 they are considered mediastinal lymph nodes and from 10 to 14 they are intrapulmonary lymph nodes.
   c. Pursuing the first mapping system the regional lymph nodes are divided into 10 lymph node stations.

Answers

1. The bronchopulmonary segments can be considered as:
   a. An independent lung unit with its own pulmonary arterial supply, pulmonary vein drainage and its own bronchus ventilation **CORRECT**.
   b. An independent lung unit with **its own pulmonary arterial supply, pulmonary vein drainage and its own** bronchus ventilation.
   c. An independent lung unit with its own pulmonary arterial supply and pulmonary vein drainage **and its own bronchus ventilation**.
2. The middle lobe pulmonary artery:
   a. Is the **first** branch arising from the mediastinal pulmonary artery.
   b. Is the first branch arising from the **mediastinal** pulmonary artery.
   c. Is the first branch arising from the mediastinal pulmonary artery **CORRECT**.
3. Find the correct sentence:
   a. The right side pulmonary lymph nodes are divided into the intrapulmonary and bronchopulmonary nodes: the **latter** are subdivided into the lobar and hilar lymph nodes.
   b. From lymph node 1 to 9 they are considered mediastinal lymph nodes and from 10 to 14 they are intrapulmonary lymph nodes **CORRECT**.
   c. Pursuing the first mapping system the regional lymph nodes are divided into **14** lymph node stations.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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The Left Lung

Piergiorgio Solli and Giulia Lai

Key Points

1. The anatomical surgical landmarks of the left lung are characterized by the architecture of the upper and lower lobes by the relative bronchopulmonary segments (5 in the upper lobe 4 in the lower lobe) and by their respective pulmonary arterial supply pulmonary vein drainage and segmental/lobar bronchial ventilation.
2. The close knowledge of the anatomy is mandatory for thoracic surgeons and this includes not only familiarity with the segmental and lobar anatomy of the (left) lung but also the understanding of the structure of the fissures the pericardium and its own recess the diaphragm and relationships between lobes and vascular structures within the mediastinum.
3. A deep awareness of the surgical anatomy and adequate mastery of lung structures is the landmark to achieve safe and complete vascular control despite the surgical complexity and an unquestionable pre-requisite to safely perform any type of left pulmonary resection (and reconstruction) as well as lung transplants.

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Introduction: General Concepts

A deep understanding of the surgical anatomy is a prerequisite to safely perform any type of anatomical pulmonary resections (and reconstruction) and lung transplant. Hereby, we report a synthesis of the core aspects of the surgical anatomy of the left lung, together with the more common anatomical variations encountered by the surgeon, with the ultimate goal to highlight the essential anatomical considerations necessary for the thoracic surgeons armamentarium.

The trachea bifurcates into the right and left mainstem bronchi at about the level of the 7th thoracic vertebra.

The left main bronchus takes off with a sharper angle compared with right bronchus and measures in adults between 4 and 5 cm in length. The bronchial tree becomes the most posterior structure when entering into the mediastinum (behind the more anterior pulmonary veins and the pulmonary artery lying in-between).

The main pulmonary artery arises to the left of the aorta and occupies a position anterior to the left main bronchus and divides into the right and left main pulmonary artery trunk. The left main pulmonary artery is shorter than the right but its extra-pericardial length up to its first branch is more than that of the right.

The pattern of division of the pulmonary arteries (especially for the left upper lobe) is

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highly variable, more than that of the bronchi and that of the veins; as a result no one definitive pattern of bifurcation for either the right or the left pulmonary artery may be described as a standard.

The venous drainage of the entire lung is guaranteed by two major venous trunks from both lungs (the superior and inferior pulmonary veins); their segmental and intersegmental tributaries form various combinations to drain into the two major trunks on both side.

The left lung is divided in two lobes—the upper and the lower lobe—separated by one fissure (the oblique or major or interlobar fissure), usually existing and well represented. Normally it begins at a somewhat higher level posteriorly, between the 3rd and 5th ribs and runs downward and forward to end in the region of the 6th or 7th costo-chondral junction. The knowledge of the location of the oblique fissure is especially important for the correct placement of the thoracotomy incision and for assignment of the utility mini-thoracotomy during minimally invasive operations [1].

The left lung is fixed at mediastinum: (a) at the level of the hilum that is composed by the left main bronchus, the left main branch of the pulmonary artery and by the superior and inferior pulmonary veins; (b) caudally by the inferior pulmonary ligament (produced by the coalescence of the inferior mediastinal parietal pleura onto the lung) usually enveloping the inferior pulmonary vein.

Each lobe is subsequently divided in the bronchopulmonary segments, that can be considered as independent lung units with their own pulmonary arterial supply, pulmonary vein drainage and its own bronchus ventilation. There are still some differences in the nomenclature for the classification of the various segments as the result of the different publications by individual investigators from North America and Europe. In 1993 Sealy et al. presented an excellent review of this topic and offered a summary of the most accepted classifications available [2, 3].

The left lung is divided in nine segments according to the more recent literature. The upper lobe presents five segments and it is divided in two large areas: the upper division that encounters three segments (apical, posterior and anterior) and the lingula with two segments (superior and inferior); while four segments are located in the lower lobe (superior, anterior medial basal, lateral basal and posterior basal).

Variations in the fissures do occur, and often part or all the oblique fissure fails to develop. Fusion of upper and lower lobe can be found when a fissure is incomplete or is largely absent and this is discovered in up to 20% of examined lungs.

Accessory fissures also do occur, and certain portions of the lung may present as deeply demarcated. A true accessory lobe is a very rare and exceptional circumstance on the left lung (more frequent on the right side), whilst accessory fissures are normally located on the planes of division of bronchopulmonary segments: this happen frequently between the lingula and the upper division in the upper lobe and for the (S6) superior segment in the lower lobe (Fig. 1).

The Left Pulmonary Artery

After the take-off from the main trunk, the left pulmonary artery ascends cranially and goes posteriorly; the intrapericardial tract is relatively short but usually completely accessible during surgery from the left hemithorax. The left main pulmonary artery passes inferior to the aortic arch and forms the superior border of the left pulmonary recess, whilst the medial border of this recess is formed by the fold of Marshall. An essential intrapericardial surgical landmark is the ligamentum arteriosum (a small fibrous ligament that is the remnant of the ductus arteriosus and formed within three weeks after birth). The release of this ligament could occasionally became significant to improve the length of the available pulmonary artery when complex procedure (reconstruction, patching) are expected with intrapericardial control and proximal left pulmonary artery clamping required (Fig. 2).

The number of branches to the upper lobe vary largely from two to seven, although

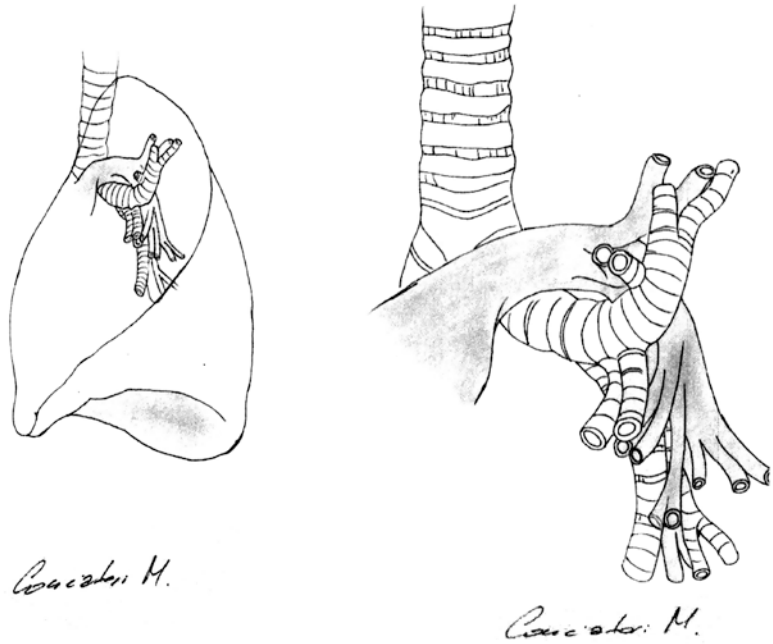

Fig. 1 Relationship between the pulmonary artery and airways of the left lung

normally the blood supply for the upper lobe is guaranteed by 4–5 branches. The take-off of these branches is from the anterior (proximally), superior, posterior and interlobar portion of the pulmonary artery.

The first segmental branch is usually the largest (truncus anterior) and supply the anterior and apical lung segments and occasionally the superior lingular division of the upper lobe. This anterior trunk is generally short, and usually appears as separate vessels arising from a common opening from the main artery.

At this stage the pulmonary artery encircles the left upper lobe bronchus to became then interlobar, and at this level a second and a third segmental branches given off to the apical-posterior segments are common; eventually the artery becomes totally interlobar and originates the lingular branch that constitutes the lingular arterial supply *in toto* in 80% of persons.

Many variations may occur in all the segmental branches, modifying this vasculature for the upper lobe, the following being the more commonly reported:

- the first anterior branch may directly supply the lingular division as well as other portions of the upper lobe, although it occurs in less than 1 in 10 individuals, this branch may carry all the blood supplying to the lingular division
- the truncus anterior may on the contrary supply only the apical segment; the anterior segment in this situation receives its arterial supply from the interlobar portion of the artery (one or two branches, shared with the lingular territory)
- in as many as 1 out of 3 persons the superior segmental branch may be distal to the lingular artery take-off and both these vessels may be multiple
- in 1 out of 7 persons, a second branch, totally separated from the trunk anterior, acts as the only lingular vessel
- finally, a vessel may arise from the common basal stem or one of its branches to contribute to the lingular blood supply.

The arterial vasculature for the lower lobe is more constant. The mediastinal artery continues

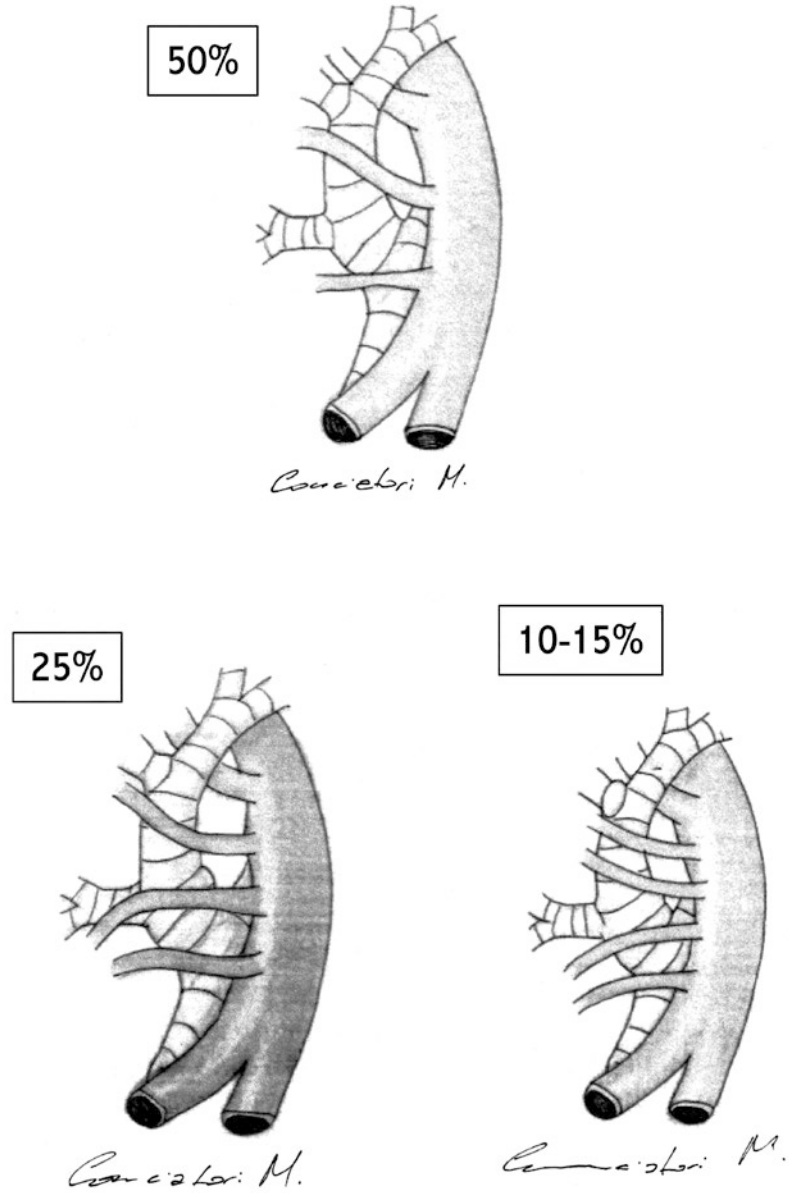

Fig. 2 Patterns of division of the segmental branches of the left pulmonary artery

in its intraparenchymal portion downward the lower lobe, becoming the common basal pulmonary artery. Posteriorly, as the artery crosses into the interlobar fissure, it branches to form a vessel going to the superior segment of the lower lobe: it is a single vessel in 78% of patients, two branches in 21% or less frequently trifurcate at a variable distance from its take-off from the mainstem arterial trunk [4]. Typically the lingular artery originates into the fissure from the pulmonary artery distal to the superior segmental artery but could be localized occasionally very close and in front.

At a variable distance from the origin of the lingular vessel, the pulmonary stem artery becomes now the common basal trunk, entirely

within the lower lobe parenchyma and subsequently divides into 2–3 branches for the caudal area of the lower lobe. The more anterior branch supplies normally the antero medial basal segment, the posterior one supplies the lateral basal and posterior basal segments, one not constant middle basal branch might supply the adjacent parenchymal areas.

The basal segmental artery usually lies posterolateral to the bronchus and again the patterns of branching of the common basal trunk and its major divisions are variable and hold importance in the case of complex lower lobe segmentectomies.

The Left Pulmonary Veins

The venous drainage of the left lung is guaranteed by two pulmonary veins: the superior and the inferior pulmonary vein. The left superior pulmonary vein lies on the anterior aspect of the pulmonary artery and as a result, it obscures the anterior branches of the artery. This vein is made up of three to four tributaries that drain the entire upper lobe: the first division is the apical posterior vein; the second branch normally represents the anterior vein (it might present up to three division: superior, inferior, and posterior); the third and occasionally the fourth divisions represent the superior and inferior lingular veins, where a single and isolated trunk may embody these veins in about 50% of persons (in an anatomical situation very similar to the middle-lobe vein on the right). The lingular vein (or veins) might occasionally drain into the inferior pulmonary vein; this variant occurs more commonly on the left side than the right with the middle lobe vein. The accurate knowledge of the venous anatomy of the left upper lobe is crucial for anatomical segmentectomies being the lingulectomy and upper tri-segmentectomy (or culminectomy) between the most frequent sublobar anatomical resection in the daily practice of a thoracic surgeon.

The inferior pulmonary vein lies posterior and inferior to the superior pulmonary vein; it usually drains the lower lobe and comprises two tributaries: the superior and the common basal branches. The first one drains the superior segment of the lower lobe whilst the second one, which is usually made up of superior basal and inferior basal branches, drains the basal segment of the lower lobe.

Unfrequently (it happens more often in the right lung) an unilateral left single pulmonary vein can be found. This condition is characterized by the joint of the superior and inferior pulmonary vein within the lung parenchyma or in the fissure forming a single trunk that before entering the pericardial sac drains the entire lung venous blood into the left atrium. This rare condition is totally asymptomatic, but it may have serious surgical implications if not recognized during an anatomic lung resection [5].

The Left Bronchial System

The left main bronchus is the most superior and posterior structure of the hilar structures of the left lung, it crosses the space below the aortic arch having the main left pulmonary artery laying on his antero-lateral surface.

The left main bronchus starts from the lateral trachea at the level of the carina and ends where the upper lobe bronchus take-off; it is 4–5 cm long and ends when its first branch arises anterolaterally as the left upper lobe bronchus. This bronchus is about 1.0–1.5 cm long and divides into superior branches and lingular branches (Fig. 3).

The superior division ascends and usually tends to separates into an apico-posterior branch and an anterior segmental bronchus; occasionally, the anterior segment migrates inferiorly to create a trifurcated pattern (bifurcation or trifurcation).

The lingular bronchus should be considered analoguous to the middle lobe bronchus; it is usually very short (0.5–1 cm logn) and divides into superior and inferior segmental lingular bronchus.

The origin of the lower lobe bronchus is very short and close to the distal part of the left upper-lobe orifice (normally less than few

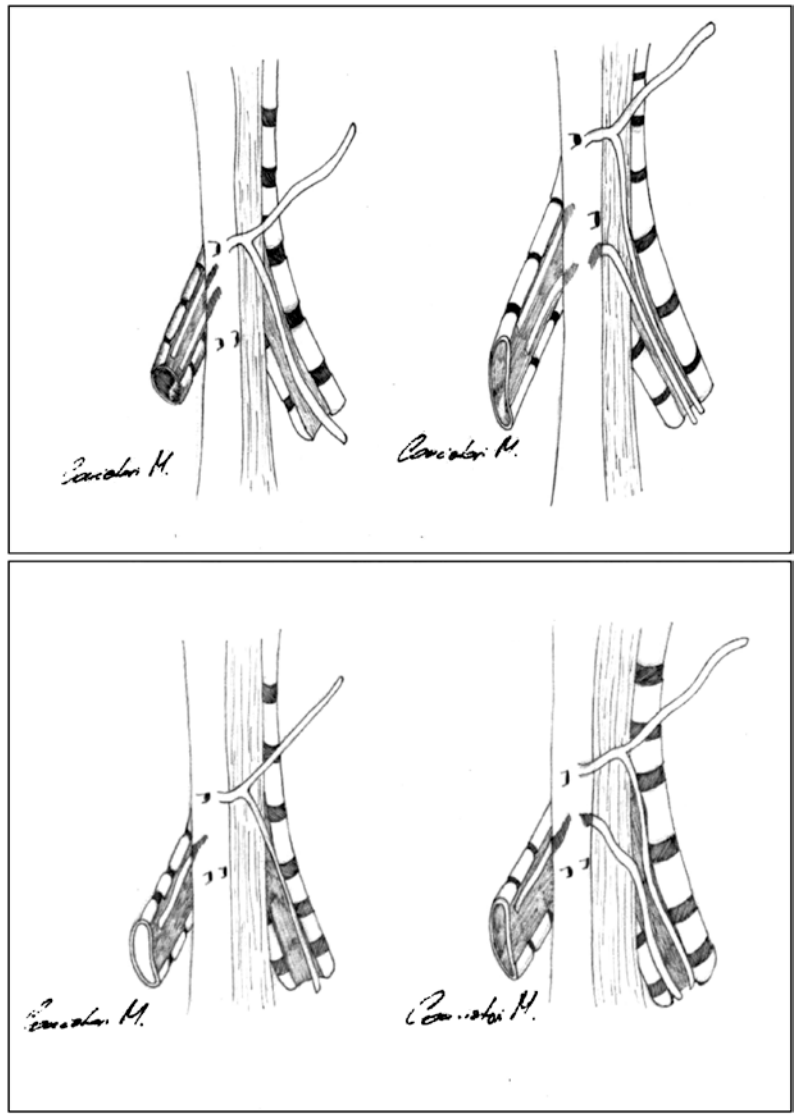

Fig. 3 Patterns of division of the bronchial artery circulation (on both side)

mm); the lower lobe bronchus gives off very soon both of its first branch: the superior segmental bronchus that runs posteriorly and the basal trunk that continues for an average distance of 1–1.5 cm as a single trunk then usually bifurcates into an anteromedial basal segmental bronchus and a common stem bronchus for the lateral basal and posterior basal bronchi.

Variations on the left side airways are exceptional and apply usually more to the distribution of the segmental bronchi from the superior and inferior divisions of the left upper-lobe bronchus and to the presence of an accessory superior bronchus arising from the lower-lobe bronchus.

As for the vasculature these deviations from normal anatomy have little clinical impact but are crucial for surgeons when dealing with different type of lobar or segmental resection of the various portions of the lung and also for reconstruction in case of broncho-plastic procedures [6].

Bronchial Arteries and Veins

The bronchial arterial system arises from the systemic circulation; the origin of the arteries is variable and has been described from the intercostal arteries, the aorta and rarely from the subclavian, innominate, internal mammary arteries and even from a coronary artery [7]. Caudwell and Coll. reported that 4 different patterns of distribution of the arterial bronchial circulation can be identified with the level of origin of the bronchial arteries from the 3rd to 8th vertebral bodies, most commonly between the levels of the 5th and 6th thoracic vertebrae, and that they arose from the descending thoracic aorta and rarely from the aortic arch [8].

On the left side, the bronchial arteries are more variable than on the right in their courses towards the left main bronchus and usually arise directly from the aorta; these arteries join the corresponding to either side and form a communicating arc around the main bronchus and from here they follow the course of the bronchus that divides as the bronchi do. The vessels are closely applied to the bronchial wall and a large networks of intercommunicating vessels are usually present. Two-thirds of this blood supply empties into the pulmonary veins and the rest goes into the bronchial veins. The bronchial veins are both either present in the mucosa or external to the bronchial cartilage. The bronchial venous drainage directs the flow to the venous plexus of the perihilar region and afterwards into the hemiazygos system [9].

The Left Bronchial Lymphatic Drainage

Anatomy

The lung presents an extensive network of lymphatic channels, originating from the loose connective tissue beneath the visceral pleura, in the connective tissue in the interlobular septa and in the peribronchial vascular sheaths. The origin of these channels is believed to be at the level of the terminal and respiratory bronchioles, where small lymphatic channels within the lobules and in the interstitial space around small blood vessels emerge from the interalveolar interstitium, creating more extensive channels and plexuses within the peribronchial tissue surrounding the airways and the blood vessels. As these channels extend proximally toward the hilar area associated with the enlarging airways and blood vessels, they form networks drain into larger collecting vessels (collectors) with thicker walls and oneway conical able to address the flow of lymph toward the hilar area in a centripetal direction.

Lymphatic channels also drain the periphery of the lung lobules in the lobular septa along with the pulmonary veins and lymphatic tissue is documented within mucous membrane of bronchi and bronchioles together with lymphatic collectors.

Map and Definitions of Stations

This lymphatic drainage pathway collect from subpleural lymphatic vessels along with lymphatic channels associated with the pulmonary veins to reach larger channels that run with the arteries and bronchi and subsequently into the segmental, lobar, interlobar, hilar and mediastinal nodes [10–12].

The left side pulmonary lymph nodes are divided into the intrapulmonary and bronchopulmonary nodes; the latter are subdivided into the lobar and hilar lymph nodes, varying in number and in location within the lung. Different maps have been published along years, including the one proposed by the International Association for Study of Lung Cancer (IALSC) [13–15] that is currently one of the most valuable for thoracic surgeons and oncologist: from lymph node station #10 to station #14 they are intrapulmonary lymph nodes and from station #1 to station #9 they are considered mediastinal lymph nodes.

The station #14 nodes are found adjacent to the subsegmental bronchi, while the segmental nodes (station #13) usually are placed at the bifurcation of the segmental bronchi and

may be associated with the segmental branches of the pulmonary arteries. The lobar lymph node (station #12) are found at the level of the carina formed by the takeoff of the different lobar bronchi and it lies nearby to the bronchus or beside the pulmonary artery; in the left lung they are most represented in the carina between the upper and lower lobe bronchus. They are all within the specific lobe.

Interlobar (station #11) nodes are usually found anteriorly at the end of the fissure in the angle between the two lobes bronchi and lying into the fissure on the interlobar portion of the pulmonary artery, where the lingular branch to the upper lobe and the superior segmental branch of the lower lobe take off. They are essentially between upper and lower lobe.

The hilar lymph nodes (station #10) lie superior to the left main bronchus and classically have been considered to occasionally extend below the aorto-pulmonary window up to the left trachea-bronchial angle, in contact distally to the paratracheal (station #4 left mediastinal lymph nodes). The boundary at this level might become unclear, although the left paratracheal area is normally very deep and difficult to reach with a lateral approach from the left hemithorax (covered by the aortic arch); the distinction between hilar and the mediastinal lymph nodes at this stage is however paramaount because it is relevant in terms of staging.

The mediastinal lymph nodes are located in the mediastinal compartment and categozide in several stations.

The supraclavicular and sternal notch lymph nodes are considered as station #1, from the lower margin of cricoid cartilage to the clavicles bilaterally and in the midline the upper border of the sternal manubrium.

Upper paratracheal lymph nodes are classified station #2. The station 2L goes from the apex of the left lung and pleural space, below the upper border of the manubrium and extends toward the superior border of the aortic arch.

Prevascular and retrotracheal nodes are known as station #3. On the left side the station #3a nodes are on the posterior space below the sternum from the apex of the chest to the level of carina in intimate contact with the edge of left carotid artery; station #3b nodes are retrotracheal from the apex to the carina.

The lower paratracheal nodes are considered as station #4. They are located in the obtuse angle between the trachea and the mainstem bronchus 4L: includes nodes of the left lateral border of the trachea, medial to the ligamentum arteriosum, with the upper border being the upper margin of the aortic arch and the lower border at the level of the upper rim of the left main pulmonary artery.

The subaortic nodes (or aortopulmonary window nodes) are named as station #5. They are Located in the area adjacent to the ligamentum arteriosum and their boundary extends from the aortic arch to the left main pulmonary artery. Subaortic nodes are lateral to the ligamentum arteriosum or the aorta or left pulmonary artery and proximal to the first branch of the left pulmonary artery and lie within the mediastinal pleural envelope.

The para-aortic nodes (also called ascending aorta nodes) are classified as station #6, located along the ascending aorta, and in the area of the lateral wall of the aortic arch or the innominate artery. Posterior boundary limited to the site of the vagal nerve. Nodes lying anterior and lateral to the ascending aorta and the aortic arch, beneath a line tangential the upper margin of the aortic arch.

Subcarinal nodes are known as station #7 and they extend from the tracheal carina to the lower border of both mainstem bronchus, they are medially placed as inferior trachea-bronchial nodes and lie in angle of the bifurcation of the trachea. Some of the subcarinal lymph nodes lie more posteriorly in relationship to the tracheal bifurcation; they are on the anterior surface of the esophagus.

The lower posterior mediastinal lymph nodes may be separate into two groups: the paraesophageal nodes (below the level of the carina) are considered as station #8, they are adjacent to the wall of the esophagus extending from the inferior pulmonary vein to the diaphragm. The pulmonary ligament nodes are known as station #9, they lie within the pulmonary ligament; they are usually two or more small lymph nodes.

Lymphatic Drainage from the Left Lung: General Concepts

The lymphatic drainage of the lobes of the lungs is primarily to the broncho-pulmonary nodes then to the hilar ones and then to mediastinal nodes. Although there are several exception to this general route and rule and as a result the direct lymphatic drainage to the mediastinal lymph nodes has been widely described [10, 11, 16] such as the well described concept of skip metastases that represents a daily practice aspect. In fact, when dealing with lung cancer, although each territory has a preference in its lymphatic spread, all the other potential routes could be used as well for lymphatic drainage and therefore this simplified classification should be considered only as a general rule.

As a general rule, the lymphatic drainage from the segmental bronchi of the left lung follows four major routes:

route 1—from the apicoposterior segmental bronchus of the upper lobe through the subaortic nodes and then in two different routes: (a) along the left vagus nerve to the left scalene nodes or (b) along the left recurrent laryngeal nerve to the highest left mediastinal nodes.

route 2—from the anterior and lingular segments of the upper lobe through the para-aortic nodes upward along the left phrenic nerve, towards anterior mediastinal nodes and to the left scalene nodes.

route 3—from any area (lower and upper lobe) along the left main bronchus to the left superior tracheobronchial nodes. At this stage the route can cross on the right side of the mediastinum through the right upper pretracheal node, or runs upward along the left side of the trachea to the paratracheal nodes and the highest left mediastinal nodes.

route 4—from the basal segmental bronchi of the lower lobe run under the left main bronchus to the subcarinal nodes. After passing the subcarinal nodes, this route extends to the right superior tracheobronchial nodes or through the lower pretracheal node to the right upper paratracheal nodes. Some branches extend upward along the left side of the trachea to the highest left mediastinal nodes [17, 18].

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Minimally Invasive Right Pulmonary Resections Techniques

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Key Points

- Minimally invasive resections techniques includes Videoassisted (VATS) and Robotic (RATS) resections.
- Videoassisted technique means true anatomic resection under screen view assistance.
- Potentially, every kind of resection con be completed in videoassisted technique.
- There are different approach to the thorax, the right one is the most familiar to the surgeon.
- The correct placement of the surgical incisions and the right position patient on the operatory table is fundamental for the success of the operation.
- The sequence of dissection is almost the same for all lobes.

Introduction

Minimally invasive thoracic surgery has become standard in many centers with survival outcomes comparable to traditional thoracotomy [1, 2] and faster rehabilitation with better and early oucomes in term of quality of life and hospitalization [3]. The advent of thoracoscopic surgery began over a hundred years ago when Dr. Jacobaeus reported his experience in the diagnosis and treatment of pleural effusions with a thoracoscope [4]. In 1978 Miller et al. described their experience using thoracoscopy in the diagnosis of thoracic disease [5]. Despite the increasing interest in thoracoscopic surgery, it was only in 1991 that the first VATS lobectomy for the treatment of lung cancer where performed in Italy by Roviaro [6]. Until now, research in endoscopic instruments continued to improve and a thoracoscope with a variable viewing angle between 0° and 120° has now been developed.

Video assisted thoracoscopic surgery is usually performed with a 30 degree rigid thoracoscope, a light source and cable, a camera and an image processor 2D or 3D and other dedicated instruments with proximal and distal articulation. Articulated staplers or vascular clips are used to divide lung parenchyma, vessels and bronchus. The use of vascular clips for proximal vascular control and energy devices for distal division of small vascular branches is recommended.

Robotic surgery is a telemanipulation system consisting of a surgical arm cart, a master console with three-dimensional view and a conventional monitor cart. It acts as remote extensions completely governed by the surgeon. The advantages are magnification of the image due to a 3D vision, more accurate movements

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avoiding physiological tremor of the surgeon, possibility of vast angulation and rotation of the instruments inside the chest cavity.

During last years, the indication for VATS lobectomy has changed and is extended today to malignant disease with tumour size <6 cm, localization in the periphery, >1 cm from a fissure or >3 cm from the lobar carina, TNM stage I or II, solitary metastasis of extrapulmonary cancer, which cannot be removed with a typical wedge resection and benign disease requiring implementation of anatomical resection. Contraindications to VATS lobectomy are relative based on the experience of the operator. Relative contraindications are previous thoracic surgery and impossibility to progress after a reasonable time with the VATS approach.

VATS Definition and Approach

There is no single standardized operative technique in performing a VATS lobectomy. The definition and technique of VATS lobectomy has been standardized after the consensus of the CALGB 39802 [7]. Usually, an operation is considered a VATS lobectomy if it meets the following criteria: a true anatomic lobectomy with individual ligation of lobar vessels and bronchus as well as hilar lymph node dissection or sampling using the video screen for guidance and no retractor use or rib spreading, only wound retractor in uniportal VATS. The thorax is entered through a variable numbers of small incisions (from one in Uniportal VATS to three or four in common VATS and four in Robotic pulmonary resections) using endoscopic instruments. Different approaches are described. The correct placement of the access incision and ancillary ports is one of the most critical aspects of performing a VATS lobectomy proficiently and is crucial for good access to upper hilar structures and lymph node stations. One of the key points is the adequate exposure of the lung, which is mandatory for every step. Also, the rotation of the surgical table and the correct retraction of the parenchyma are essential to improve the exposure and to obtain different angles of view. During last years, different approaches to VATS lobectomy, port placement and surgical technique have been described and the choice depends on surgeon attitude and preference [8–13] (Table 1).

Anterior Approach

The authors prefer the anterior three-port approach (Fig. 1) to perform a lobectomy. The first surgical incision is a 10 mm anterior axillary incision along the 7th to 8th intercostal space for the thoracoscope (10 mm 30° thoracoscope). When the camera is inserted, the surgeon can explore the pleural cavity to evaluate metastatic disease or any contraindication to VATS resection. If the lesion is small or cannot be easily palpated, knowledge of segmental anatomy is crucial for determining the location of the lesion within the segment(s) of the respective lobe. If the procedure can continuous by VATS approach, the second incision can be done anteriorly at the fifth intercostal space (4 cm) and is used for hilar dissection and to remove the lobe.

The third and last incision is finally performed on the 6th or 7th intercostal space, in line with the oblique fissure, in a straight line down from the scapula tip and anterior to the latissimus dorsi muscle, at the posterior axillary line. This access is usually used to introduce an endoscopic retractor during hilar dissection and for mediastinal lymph node dissection, when the lobe has been removed. A wound retractor can be used for soft tissue retraction. Endoscopic linear staplers are used for individual vessel and bronchial ligation. Bronchus can be divided also with a TA stapler. At the end of the operation, the lobe is placed in a specimen bag to be removed.

Uniportal Approach

Single-incision video-assisted thoracic surgery (VATS) lobectomy follows the oncological principles of major pulmonary resections by VATS: individual dissection of veins, arteries and lobar bronchus, fissure usually for last and complete

Table 1 General data of different approaches and techniques

Technique	General approach	Recommended approach for stapler of structure
Anterior 3-incisions [8, 9]	• Bronchus or fissure last • View from inferior or anterior port if necessary for anterior upper lobes structures	Inferior: • Superior and inferiorpulmonaryveins • Upperlobearteries • Upperlobebronchus Utility: • Minor fissure Anterior: • Middle lobeartery and vein • Lower lobearteries • Lower lobebronchus • Major fissure
Anterior 2-incisions [10]	• Fissure last • View from inferior port switched to utility port for antero-superior structures	Inferior: • Superiorpulmonaryveins • Upperlobearteries • Upperlobebronchus Anterior (utility): • Inferiorpulmonaryvein • Middle lobeartery and vein • Lower lobearteries • Lower lobebronchus • Fissures
Posterior 3 incisions [7, 11]	• Bronchus last • View from inferiorport • Posterior port used for retraction, dissection and stapler passages	Posterior: • Superiorpulmonaryvein • Upperlobearteries • Upperlobebronchus • Middle lobeartery and vein • Fissure Utility Anterior: • Inferiorpulmonaryvein • Lower lobearteries • Lower lobebronchus
Posterior 3-incisions [12]	• Fissure last • View from inferiorport • Utility incision for stapler in fissure division	Posterior: • Superiorpulmonaryvein • Upperlobearteries • Upperlobebronchus • Fissure Utility: • Inferiorpulmonaryvein • Middle lobeartery and vein • Lower lobearteries • Lower lobebronchus • Fissure
Uniportal [13]	• Fissure last • All instruments through single port incision • Surgical trauma to a single intercostals space	• All viewing and dissection through a single port • Camera: posterior part of the incision • Instruments and staplers: anterior part of the incision
Robotic	• CO_2 inflation • Nodes first • Fissure last	• 3 arms • Camera port • Assistant port

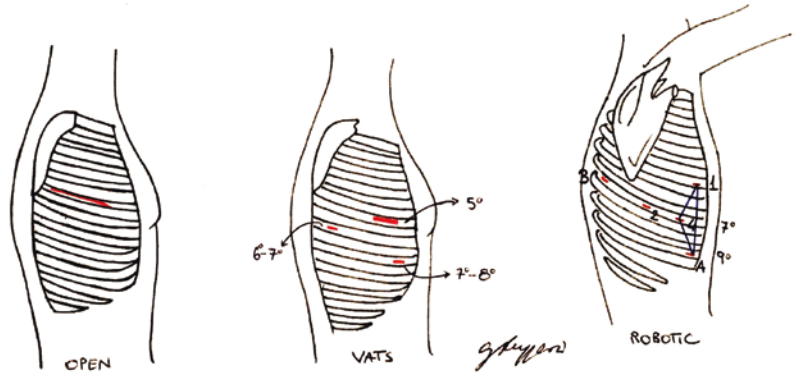

Fig. 1 Different approach to the thorax

mediastinal lymphadenectomy. The utility incision is usually placed in the 5th intercostals space. No trocar are required. Sometimes ribs spreader are used. The surgeon and the assistant are placed in front of the patient, so they have the same field of vision and the coordination is better. Sihoe AD described a "traffic light" configuration for the correct position of the instruments during uniportal VATS surgery: the video-thoracoscope should be kept at the top "red light" position while the left- and right-hand instruments are inserted at the "yellow light" and "green light" positions. If needed, the scope may be relocated at the "yellow" or "green light" positions for specific view [14, 15]. The resected lobe is delivered out in a specimen bag. A chest tube (20Fr or 24Fr) is inserted directly trough the uniport and anchored.

Robotic Approach

In robotic surgery is foundamental the correct configuration of the operating room. The surgeon console should be positioned near the patient-side team so that communication with other surgeon is good, even if the Da Vinci surgical system console contains a microphone. The presence of a second console permits easy exchange of control between surgeon and allow resident/fellow training. The robot is driven over the operatory bed and patient's head on a 15-degree angle to open up robotic arm 3 over head and shoulders. Monitors are in front of the assistant which stand in front of the patient. The ports are all inserted in the seventh intercostal space for upper and middle lobectomies and in the eight intercostals space for lower lobectomies (Fig. 1):

- 5 mm port Robotic arm 3: 1–2 cm laterally from the spinous process of the vertebral body, for thoracic grasper
- 8 mm Robotic arm 2: 10 cm medially to arm 3, for blunt instruments as Cadiere graspers (right hand of the surgeon) and for stapler insertion
- 12 mm Camera port and CO_2 inflated port: 9 cm medially to arm 2
- 12 mm Robotic arm 1: above the diaphragm anteriorly, for bipolar curved thoracic dissector (left hand of the surgeon) and for stapler insertion
- 12 mm Assistant port: as lower as possible triangulated with arm 1 and Camera port, and eventually for stapler insertion.

In robotic right lung resections surgery, mediastinal limph nodes dissection is usually performed prior to lobectomy, it start dividing the pulmonary ligament with lymphadenectomy through the posterior mediastinal reflection and continuous with hilar lymphadenectomy to facilitate removal nodes station from lower ones (9-8-7) to upper ones (2R, 4R). The rationale is to expose the vessels and the bronchus

prior their dissection. The specimen is removed through the assistant port in an endo-bag inserted in arm 3 and one chest tube (20Fr or 24Fr) is placed via the most anterior port (arm 1 in right surgery).

Right Anatomical Resection Techniques

The patient is positioned on the operatory table in left lateral decubitus position. The hands are placed without support in the "prayer" position in front of the face of the patient or with the arm abducted at 90° and the operating table is manipulated to extend the thorax opening up the intercostal spaces. Both the surgeon and assistant stand on the anterior (abdominal) side of the patient with the surgeon positioned cranially. The surgical access are placed and, for the right side, the utility incision is usually placed in the anterior axillary line, over the anterior hilum (about 5th intercostal space) in the cases of upper lobectomy or an interspace or two lower (adjacent to the major fissure) for middle and lower lobectomies. The sequence of dissection is the same for all lobes making it an easier technique to teach. The first structures to be transected are the major vessels. To prevent air leaks there is minimal handling or dissection of the fissure. The surgical procedure is facilitated aligning the view of the camera with the general direction of the dissection. This is most easily achieved with angled view cameras, at 30 or 45 degrees from the long axis of the scope. This also allows the surgeon to explore the hilum with the camera even if in a trocar site low in the chest. It is important for the surgeon to remember that occasionally a better view may be available by placing the camera in the access or posterior incision: flexibility with the operative technique is foundamental to reduce the complexity of the procedure. Pulmonary vessels are dissected with a 30-mm endovascular stapler. Bronchi are ligated with 45-mm endoscopic staplers, although a "TA" type stapler may be used for the bronchus. It is important to introduce the stapler into the chest such that, once around the vessel or bronchus, it exits into "safe plan" and is not encumbered by other structures. This will avoid injury to other tissues and vessels, and assure a secure closure of the target. Bronchial arteries may be cauterized or clipped. Fissures are typically divided with endoscopic GIA stapler.

Specimen removal is achieved with the use of a specimen bag, to minimize contact with the soft tissues at the access incision site. In that way, the incidence of "port-site" recurrence has been reduced. Prior closing the incisions, usually an intercostal nerve block is performed and the chest tube (usually one, 24 Ch or 28 Ch) positioned.

In the posterior approach, the initial maneuver is to identify the right after lobe bronchus from the posterior mediastinum and perform a significant dissection in the area of the junction between the upper lobe bronchus and the intermediate bronchus. In that way the anterior hilum dissection is usually not necessary, but especially in right lung surgery, it is important to understand the segmental anatomy of the pulmonary veins viewed from the anterior hilum. The pulmonary veins are the anterior structures in the hilum. Their tributaries are also anterior to the segmental arteries and bronchi. The interlobar vein often traverses between the upper and middle lobes in the horizontal fissure before joining the superior pulmonary vein in the hilum. Often, the middle lobe vein drains into the right superior pulmonary vein. Nodal dissection may be performed either before or after completion of the pulmonary resection. Initial dissection often facilitates the subsequent lobotomy by increasing the mobility of the specimen at the hilar level. Furthermore, identification of N2 disease, previously unrecognized, would allow for induction therapy before complete the lung resection. On the other side, access and removal of the various nodal stations is usually easier after the pulmonary resection or during the ligation of the various hilar structures.

An advanced knowledge of the surgical anatomy is fundamental to perform video assisted lung resection safely (Figs. 2 and 3).

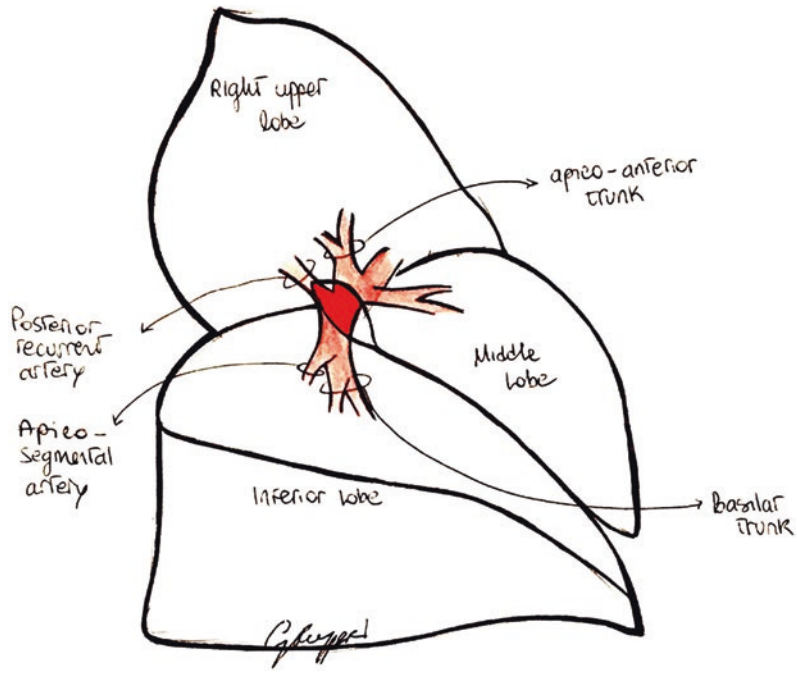

Fig. 2 Anatomy of the right pulmonary artery, view from the fissure. Pulmonary artery is revealed by separating the overlying pleura using blunt dissection

Right Upper Lobectomy (RUL)

Although variable, one approach to the structures of the right upper lobectomy is to begin with the dissection of the pulmonary vein, than the truncus anterior of the artery or Boyden truncus, the upper lobe bronchus, the posterior ascending artery and completation of the horizontal and oblique fissures.

Pulmonary vein dissection: Our approach to right upper lobectomy begins with the dissection of the mediastinal pleura, just behind the frenic nerve that must be recognized and avoid. The upper lobe pulmonary vein is recognized and circumferentially dissected, care must be taken to identify and preserve the middle lobe pulmonary vein: the middle lobe vein is one of the more common anatomic variants seen in vein anatomy. A vessel loop is then used to encircle the superior pulmonary vein and space is created to pass a 30-mm endovascular stapler from the lower posterior port.

Pulmonary artery dissection: Even if the lobe pulmonary artery anatomy is variable, the main pulmonary artery usually lies immediately deep to the pulmonary vein and once divided the pulmonary vein, the apical branches of the pulmonary artery are identified. The anterior trunk (Boyden trunk) is prepared with a curved forceps or right angle clamp and then encircled with vessels loop and divided with an endovascular stapler placed through the lower posterior port. The pulmonary artery is now identified creating a tunnel over the ongoing pulmonary artery in the fissure and allows sufficient exposure of the posterior ascending artery. During this passage, the camera is positioning through the anterior port and lung retracted posteriorly using typically the posterior inferior camera port. The lung is stretched to the chest wall and the minor fissure is partially completed with a tissue load of the stapler up of the confluence of the veins. The posterior ascending artery can be transected at this moment, if identified, with an endovascular stapler introduced by the posterior working incision, or after the bronchus. In that case, as it usually runs just behind the upper lobe bronchus, it can be injured (Fig. 4).

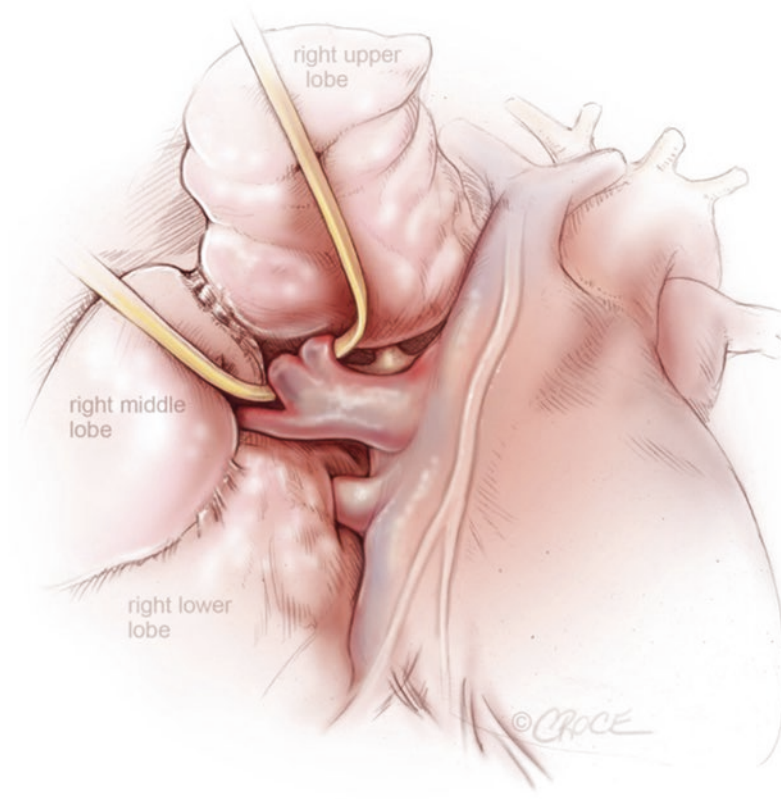

Fig. 3 Right superior pulmonary vein from right upper lobe is encircled by a vascular loop, while the pulmonary venous drainage from the right middle lobe is clearly seen (from Ref. [9])

Bronchus dissection: After the intermedius bronchus has been identify, the right upper lobe bronchus can be transected using a thick tissue endostapler through the posterior port. A small inflation test of the middle and lower lobes can be performed before the transection of the bronchus to ensure that the stapler is placed correctly. Is not rare to encircled the right main stem bronchus inadvertently especially in small body habitus patients. If the posterior ascending artery has not been previously transected it can be done now with an endovascular stapler introduced by the posterior working incision and the oblique fissure can be completed.

Fissure: The remaining part of the minor fissure between the upper and middle lobes is than dividing with an endoscopic stapler in the working incision. Is important in that phase to remove the entire upper lobe.

Technical variations:

- *The "fissure less" or "fissure last" technique* for right upper VATS lobectomy uses an "anterior to posterior" approach, where dissection proceed from the anterior structures in the hilum to the posterior structures, dividing the fissures for last. The lung is retracted towards the back and the right upper vein is dissected for first. The pleura is incised around at the top of the hilum until the intermedius bronchus posteriorly, it allows the dissection of the anterior trunk of the artery, which is divided and allow improved retraction of the lung posteriorly exposing the upper lobe bronchus and the posterior ascending artery that can be now dissected. The dissection proceeds along the ongoing pulmonary artery to exclude

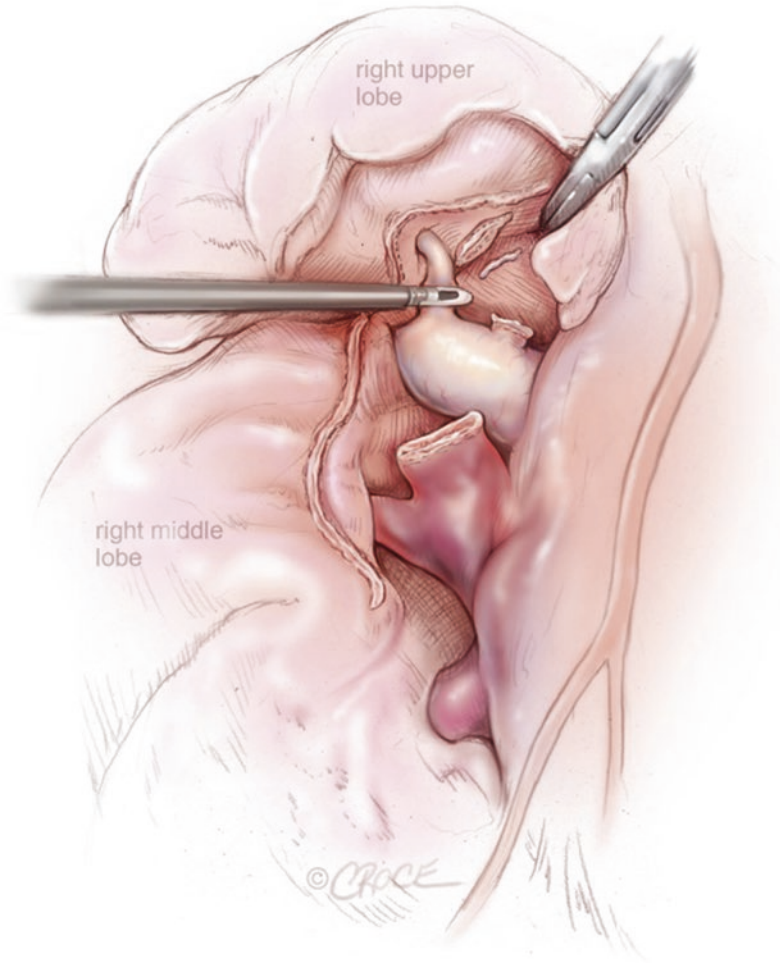

Fig. 4 After division of right upper lobe pulmonary vein and truncus anterior, posterior ascending segmental artery to the right upper lobe is being divided (from Ref. [9])

accessories branches and to avoid the middle lobe branches and the minor and oblique fissures are divided. The rationale of the "fissure less" or "fissure-last" technique with diathermy or ultrasonic device or with stapler is to avoid air leak after surgery.

- *The "uniportal" technique* for upper lobectomies includes two options to start the dissection based on the distance between RUL vein and anterior trunk: if the distance is enough to allow the stapler insertion, the vein is dissected and divided for first followed by the artery; if the distance is too short or the angle for the stapler insertion is not optimal, the artery is divided first and then the vein. Once the artery is divided, the lung is retracted laterally and posteriorly allowing a clear view of the RUL bronchus, exactly where the trunk was and it rises vertically just above the azygous vein. The broncus is divided with a thin stapler or cutting the bronchus and suturing the proximal stump, especially for lobectomies requiring bronchoplasty or sleeve resection. Now, with the same lung retraction, the posterior ascending branch(es) of the artery is visible and is dissected with stapler or vascular clips. The fissures with the middle and lower lobe are finally dissected in a "fissure-less" or "fissure-last" technique.

- *The "robotic" approach* of RUL start, as previously stated, opening the posterior mediastinal pleura and with lymphadenectomy. The superior pulmonary vein is than encircled with the vessel loop and divided followed by the anterior trunk of the right artery. The right upper lobe is than reflected anteriorly to expose the bifurcation of the main stem bronchus. The right upper lobe bronchus is encircled and divided. As in conventional VATS and Uniportal VATS, care must be taken to apply in this phase minimal retraction on the specimen to avoid tearing the remaining artery branch(es), which is finally dissected. The fissures are divided.

Middle Lobectomy (ML)

The middle lobectomy start, as the right upper lobectomy, with the incision of the mediastinal pleura to identify the superior pulmonary vein that is always dissected for first. A completely "fissure-less" technique for ML is not possible, due to the location of the lobe between the upper and the lower lobes. However, the minor fissure is usually divided for last.

Pulmonary vein dissection: The lung is retracted posteriorly and the confluence of the middle lobe and upper lobe vein is identified. Is very important to identify also the inferior pulmonary vein according to the frequent anatomy variation seen in the middle pulmonary vein. Once the middle lobe vein has been mobilized and prepared with an angled clamp, an endovascular stapler is passed through the posterior port and the vein is divided.

Bronchus dissection: Now the middle lobe bronchus, which lies just behind the vein, is well exposed and can be mobilized through the utility access incision. Commonly there are, as in the other lobectomies, lymph nodes surrounding the bronchus that, once removed, facilitate the dissection of the junction between the middle lobe bronchus and the lower one and its division with a 45 mm stapler or a 30 mm endovascular stapler because of its thickness. Caution should be used during division of the bronchus because of the underlying artery branch(es) to the middle lobe (Fig. 5).

Pulmonary artery dissection: The two fissures between the upper and the lower lobe separate the middle lobe. The middle pulmonary artery is easily identified after the dissection of the anterior part of the major fissure that can be open. Attention should be paid to avoid transecting segmental arteries to the lower lobe. Once the middle artery branch(es) is exposed, it can be gently encircled and transected with an endovascular stapler (Fig. 6).

Fissure: The remaining posterior part of the major fissure and the minor fissure are finally divided with a stapler through the utility incision.

Technical variations:

- *Port placement*: Some authors suggests a different port placement in middle lobectomy with a port above the utility incision, at 4th intercostal space, and the camera port as usual at the 7th or 8th intercostal space on the median axillary line, in this technique the stapler for the resection of the artery is inserted through the upper port [16] (Fig. 7).
- *The "uniportal" technique:* The basic approach is similar to the RUL and the sequence of dissection is typically pulmonary vein, lobar bronchus, pulmonary artery and fissures using an anterior-to-posterior approach. The challenge in ML is that the hilum is near to the vessels of the other two lobes and for that the head of the stapler is difficult to handle between this structures from the uniportal access. Gently manipulate the lung with one hand holding the retractor could help to allow the insertion of the stapler or dissecting instruments with the dominant hand.
- *The "robotic" approach:* The middle lobe is retracted laterally and posteriorly with robotic arm 1 and the hilum is exposed. The bifurcation between the upper and middle lobar veins is identified and prepared taking care to the underlying pulmonary artery. The

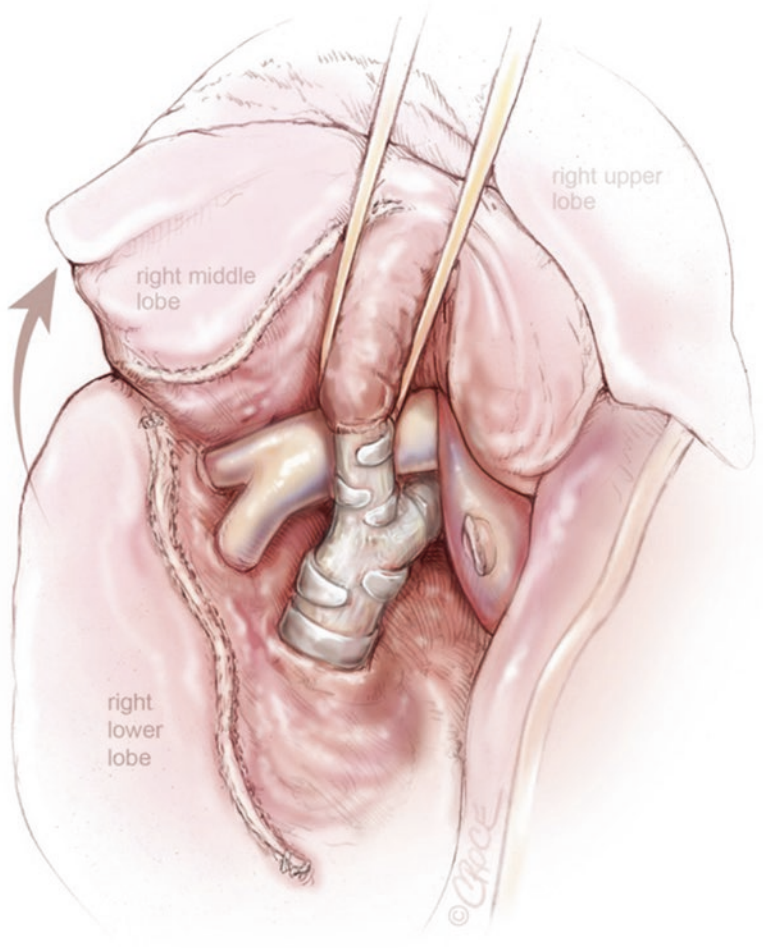

Fig. 5 Bronchus of the right middle lobe is presented through the oblique fissure after division of the right middle lobe vein (from Ref. [9])

middle lobar vein is encircled and divided. The major fissure is divided from anterior to posterior, if not complete. The middle lobe bronchus is than isolated running from left to right in the fissure and prepared avoiding injuries of the middle lobe artery that is located just behind it. This is the moment in which hilar lymphadenectomy is performed and the bronchus is divided. Dissection of the fissure continues posteriorly until the branches to the superior segment are identified, and the branch(es) of the middle artery are isolated and divided. In robotic approach, the stapling of the middle lobar structures is facilitated by passing the stapler from posterior to anterior, this allow a major working distance. Finally, the minor fissure is divided and the specimen removed.

Right Lower Lobectomy (RLL)

The right lower lobectomy usually start with the dissection of the inferior pulmonary ligament with electrocautery and the lung retracted superiorly. Often there is a lymph node in the inferior pulmonary ligament near the vein and it can be considered an indicator that the vein is just above.

Pulmonary vein dissection: The pleura is mobilized posteriorly and anteriorly to allow

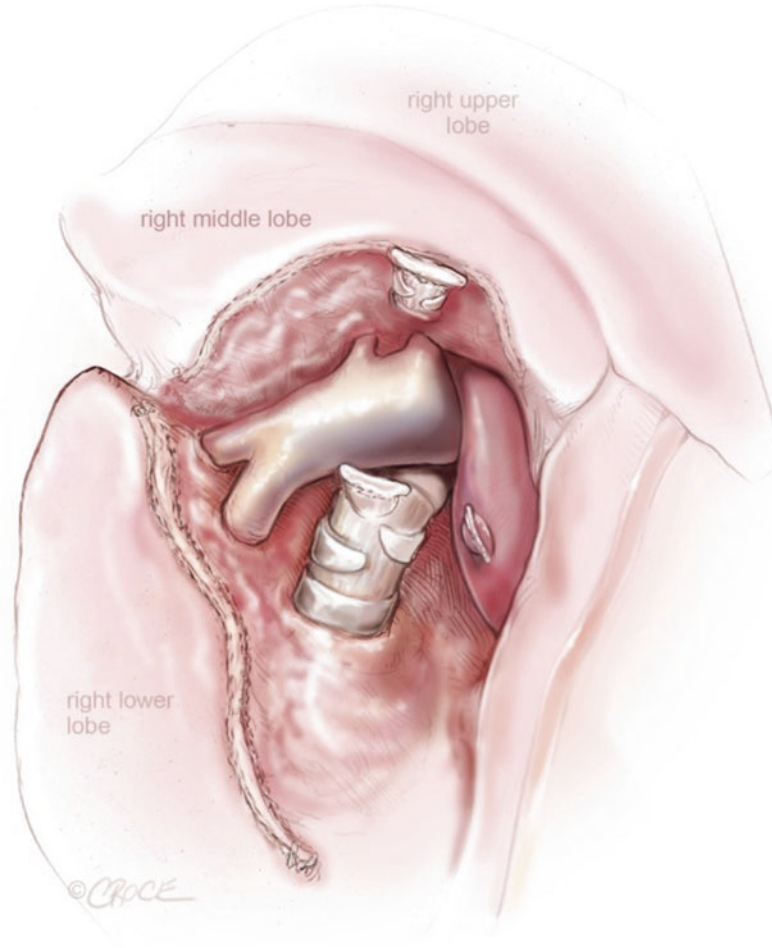

Fig. 6 After the division of the right middle lobe vein and bronchus, pulmonary artery branches to the right middle lobe and lower lobe is exposed (from Ref. [9])

the mobilization of the inferior pulmonary vein with blunt dissection using a pediatric suction device. With lateral retraction of the lobe the vein can be encircled with a right angled clamps. It is fundamental to recognize the middle lobe pulmonary vein before sectioning the inferior pulmonary vein, as it can occasionally drain into the inferior pulmonary vein. The vein is then dissected by introducing the endovascular stapler through the working incision, which is usually performed for lower lobectomies just above the confluence of the lower pulmonary vein (Fig. 8).

Bronchus dissection, pulmonary artery dissection and fissure dissection: The sequence of the dissection depends on the anatomy of the fissure: if the major fissure is complete and the pulmonary artery is visible it is reasonable to dissect and divided the artery for first. Care should be taken to ensure that there is no variation in the arterial supply to the lower lobe such as an ascending posterior branch that needs to be eventually identified and divided. The anterior portion of the fissure can be transected once the artery is identified as usual.

The right lower bronchus is located immediately behind the pulmonary vein, in front of the pulmonary vein. A caudal traction on the bronchus can allow a better explosion of the structure and the application of the stapler. The middle

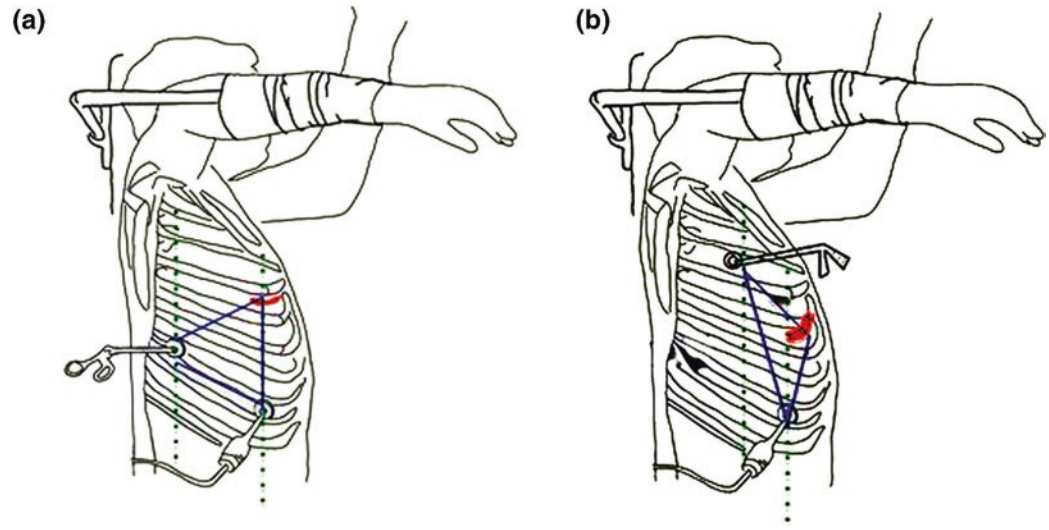

Fig. 7 Videothoracoscopic technique. (**a**) Right upper and lower lobectomy. (**b**) Middle lobe lobectomy (from Ref. [16])

lobe bronchus should be identified before transect the inferior bronchus and the endoscopic GIA stapler is inserted, usually through the working incision, avoiding the middle lobe bronchial orifice. Testing the inflation of the middle lobe while the stapler is closed across the lower bronchus can avoid damage to the middle lobe.

If the major fissure is incomplete and the access to the artery is not so clear, it can be appropriate to dissect the pulmonary artery after the bronchus has been dissected and transected through the lower port.

Technical variations:

The vantage point for lower lobectomies is the traditional posterior-inferior port, even if many surgeons prefer the utility incision for stapler insertion.

- *The "fissure last" technique* is a popular approach for lower lobectomies. The vein is dissected for first and the lung retracted superiorly to expose the airway. The dissection proceed close to the bronchus and the artery is safely exposed and divided. Until the surgeon becomes familiar with viewing the artery from this approach, care must be taken to avoid the bleeding or occlusion of branches destined to the upper lobes. Once divided the bronchus and the artery, only the fissure remains.
- *The "uniportal" technique:* The basic approach is similar to the standard VATS lower lobectomy. The lung is retracted cranially and laterally and the pulmonary ligament is exposed and dissected. The inferior pulmonary vein is looped and divided. Unfortunately, the stapler tip could posteriorly hurt the spine and to avoid this the lung is retracted forward and the tip of the stapler is articulated toward the cephalic direction. After the vein is divided, the lung is retracted toward the feet and the oblique fissure is completed. This exposes the pulmonary artery in the fissure, which is dissected until the top of the fissure where an interlobar lymph node, present in almost patient, is a useful landmark of the bifurcation between RLL and RML pulmonary arteries. Once the artery is divided, retraction of the RLL laterally and posteriorly allows the vision of the RLL bronchus from the bronchus intermedius. The lower lobe bronchus is than dissected and the stapler inserted from a right-to-left direction to divide it.
- *The "robotic" approach:* Robotic right lower lobectomy start with the dissection of the

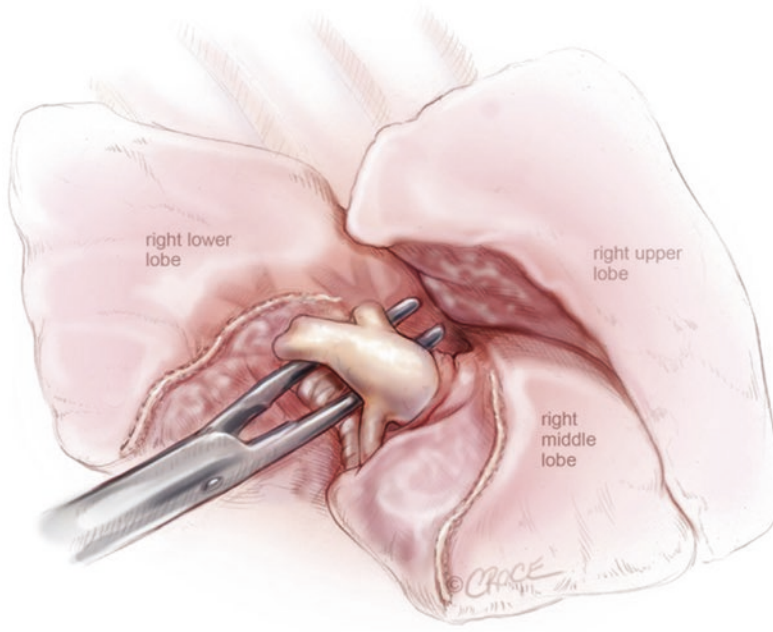

Fig. 8 Pulmonary artery to right lower lobe, including superior segmental artery is isolated, after dividing the oblique fissure anteriorly (from Ref. [9])

inferior pulmonary ligament to expose the bifurcation of the right superior and inferior pulmonary veins but the vein is not dissected for first. The robotic dissection continues along the major fissure, that is divided with stapler if not complete and a subadventitial plane on the ongoing artery is established. The ascending posterior branch of the artery and the middle artery are identified and the ascending posterior artery is divided. The common trunk of the right lower lobe artery is looped and divided followed by the inferior pulmonary vein. The right lower lobe bronchus is isolated, taking care of the middle lobe bronchus, dissected and divided as usual.

Superior Bilobectomy

Thoracoscopic superior bilobectomy is performed as a RUL plus a ML.

Inferior Bilobectomy

Thoracoscopic inferior bilobectomy is performed as a ML plus a RIL.

Right Pneumonectomy

A VATS or RATS approach for pneumonectomy has been discuss for a long time due to the hilar extension and size of the primary lung cancer. Reports from high volume centers have demonstrated its feasibility. Another hurdle is the specimen removal through the working incision that is often smaller than the specimen and should required an enlargement. Due to this consideration, the authors suggest to perform pneumonectomies in minimally invasive technique only if the surgeon is expertise and only after that the patient, the tumour and the mediastinum have been largely evaluated.

The surgical technique for thoracoscopic right pneumonectomy usually start with the dissection of the inferior pulmonary ligament and the incision of the mediastinal pleura anteriorly to expose both pulmonary veins. Isolation of the veins within the pericardial cavity is often necessary and helpful. The veins are separated with vascular stapler. The pulmonary artery is separated from the main stem bronchus and can be encircled with a vessel loop to facilitate the passage of the stapler across the artery. During the preparation of the main stem bronchus, care must be taken to avoid any peribronchial or adventitial tissue that might impede the stapler passage. The artery and the bronchus are divided as usual. Coverage of the bronchial stump is routinely performed to minimize the risk of a bronchial fistula with intercostal muscle flaps, thymic or pericardial fat or pleural fat. As for open right pneumonectomy the risk for postoperative failure is high, but, compared with left pneumonectomy, is technically easier according to the better exposition of the main pulmonary artery and right main bronchus.

Right Sleeve Pulmonary Resection: Right Upper Lobe Sleeve Lobectomy

Thoracoscopic sleeve pulmonary resections are rare even if feasible, and, as pnumonectomies, should be performed only by expertise surgeons. A lot of VATS surgeons suggest to perform arterial sleeve resection with a thoracotomic approach according to the high risk of damage to the artery.

Preoperative bronchoscopy is done to determine where the bronchus needs to be cut with oncological clear margins and often a mediastinoscopy for complete node dissection is performed the same day of the sleeve resection.

Right sleeve pulmonary lobectomy usually require 4 thoracoscopic access:

1. 2 cm long at the 6th intercostal space on the mammary line
2. 8th intercostals space in the posterior axillary line
3. 4 cm utility incision directly up the superior pulmonary vein, anteriorly of the edge of the latissimus muscle
4. 2 cm long at the 7th or 8th intercostals space slightly posteriorly the tip of the scapula.

The lung is retracted posteriorly, the hilum is explored opening the mediastinal pleura anteriorly and the lymph node at level 10 is removed. The right upper lobe vein and the middle vein are identify and the upper lobe vein is stapled through incision 4. If not complete, the minor fissure is complete with a stapler through incision n° 1. The lung is retracted posteriorly and inferiorly and the anterior trunk of the artery is stapled with a vascular stapler through incision 4 and clips or stapler are used to close the ascending branch of the artery for the upper lobe. The major fissure is now completed and the bronchus is the structure leave for last. The right mainstem bronchus is better exposed retracting the pulmonary artery with a vessel loop inferiorly. The right main stem bronchus is prepared removing any peribronchial or adventitial tissue and the bifurcation between the upper lobe bronchus and the intermediate bronchus is visualized. Through the utility incision, a n° 15 blade is inserted to cut the main stem bronchus and the intermediate one. The upper lobe is removed. A stay suture is placed at the junction of the cartilage and membranous portion of the intermediate bronchus and the mainstem and the intermediate bronchus are sutured together with 3-0/4-0 PDS or Vycril stitches. The membranous portion is done for first, followed by the sides and the cartilagineous ones. At the end of the procedure, the anastomosis is tested for airleak.

Self-study

(A) Which statement is true:
- (1) There are no absolute contraindication for VATS lobectomy.
- (2) Only lesions <4 cm can be resected in videoassisted technique.
- (3) Central lesions are usually resected by Uniportal technique.

(B) Which statement is true:
Right pulmonary lobectomies needs transection of major vessels and lobar bronchus:
(1) Artery for first, than vein and bronchus.
(2) Vein for first, than artery and bronchus.
(3) Bronchus for first, than vein and artery.
(4) The sequence of vessels and bronchus dissection and transection is variable according to the different technique and surgical access.

Answer

(A)

(1) CORRECT: Potentially every resection can be completed in minimally invasive technique.
Relative contraindications are previous toracica surgery and impossibility to progress with the VATS approach.
(2) Nowadays, 6 cm is considerevole the site limit for VATS resection.
(3) Central lesions are usually removed in open technique.

(B)

(4) CORRECT: Most author prefer to transect the artery for first, than the vein and the bronchus, but there is not a standardized rule and the sequence depends on the surgeon and on the different access (VATS vs RATS) and approach (Uniportal vs Triportal anteriore or posterior) (Table 1).

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Minimally Invasive Left Pulmonary Resections Techniques

Jury Brandolini and Piergiorgio Solli

Left Anatomical Resection Techniques

All operations are performed under general anaesthesia with single lung ventilation. The patients are placed in right lateral decubitus position with arms flexed toward the head and rotated slightly posteriorly, so the anterior axillary line is presented toward the ceiling. The surgical table is flexed in wedge-shaped position to obtain maximum separation of the intercostal spaces. A 30-degree scope is used to allow visualisation of hilar structures from multiple perspectives. Multiple approaches to performing VATS lobectomy are described, with port placement dependent on surgeon preference. In the fissure-last VATS lobectomy technique, hilar bronchovascular structures are dissected and divided first; oblique fissure is transacted at the last step using a stapler. This approach appears to be a superior technique to traditional VATS lobectomy regarding preventing postoperative air leak and reducing hospital stay [3].

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Left Upper Lobectomy

Normally, the approach to the upper lobectomy is to perform the hilar dissection, posterior pleura incision and dissection to identify a "landing zone", to proceed with an anterior to posterior approach [1, 2]. After inspection of the pleural surface to confirm the absence of metastasis; lung is retracted posteriorly, and mediastinal pleura is open widely along the anterior hilum, superior pulmonary vein and continues upward around the pulmonary artery extending the dissection posteriorly. After dissection of the ligament, the left upper vein is isolated first (Fig. 1); care must be taken to identify the lower lobe vein in the presence of common left vein (23.9% of cases) that can result in accidental pneumonectomy [4]. The superior vein is encircled with a vessel loop and divided with a 30–45 mm vascular stapler. The next step is the identification and division of the anterior artery (Fig. 2). VATS approach such an anterior to posterior approach allows ready exposure of the first two to three arterial branches to the upper lobe. The lobe is retracted posteriorly and towards the diaphragm to dissect the AP truncus using blunt dissection. Then the lobe is pulled up to the apex to open the space behind the artery; vascular stapler can be now safely introduced for the PA anterior trunk division. Once the artery is divided, removal of lymphatic tissue helps in the identification of the saddle between the upper lobe

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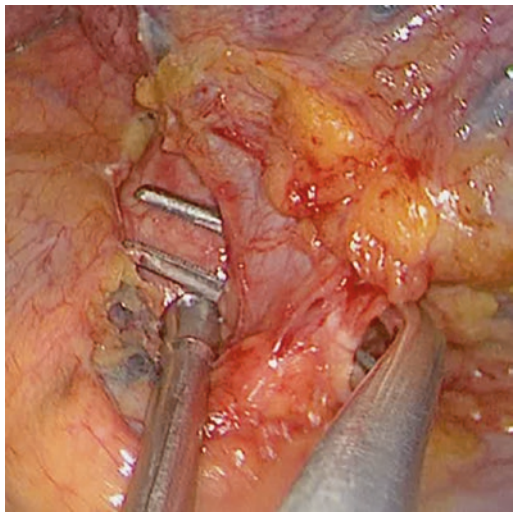

Fig. 1 Dissection of the upper lobe vein

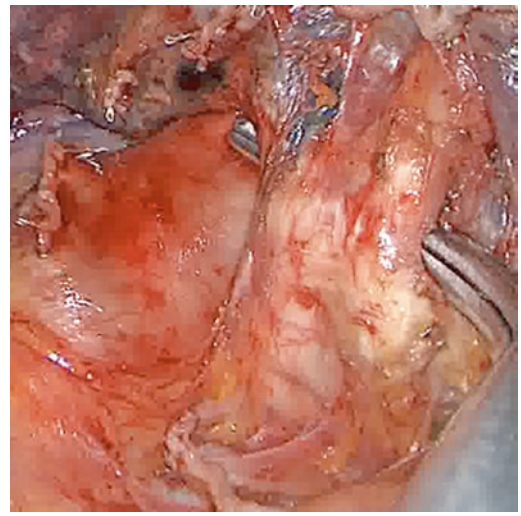

Fig. 3 Dissection of the upper bronchus

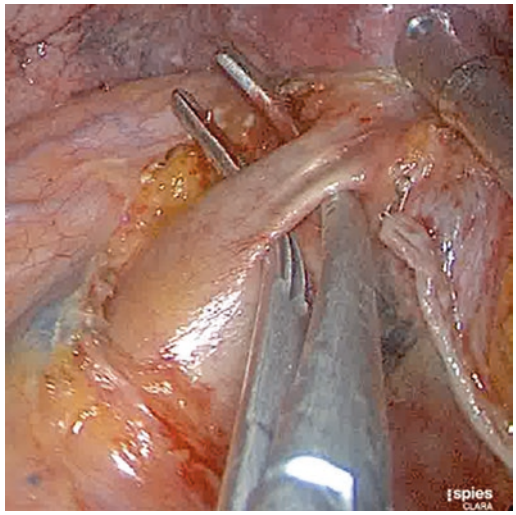

Fig. 2 Dissection of the mediastinal artery

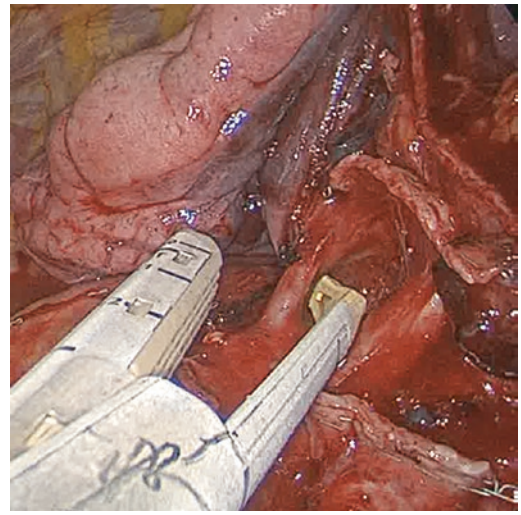

Fig. 4 Division of the arterial branches for the upper lobe

and lower lobe bronchus. The lobe is now pulled anteriorly and upward, thus to expose the upper lobe bronchus that arises vertically from the main PA (Fig. 3); a stapler passed from the inferior thoracoscopic port is used to close and divide the bronchus. Completion of the anterior part of the fissure may enhance the exposure of the lingular artery. With the PA exposed, the remaining arterial branches to the upper lobe and the lingular branch can be identified and dissected by the vascular stapler (Figs. 4 and 5). Now, the lobectomy is completed by separating the upper lobe from the lower lobe, transecting the fissure with a 60-mm stapler, according to the fissure-last technique (Fig. 6). An alternative fissureless technique, called "tunnel technique" is described by Decaluwe H.; this procedure reduces the risk of postoperative air leak and obtains a good N1 nodal dissection before the division of the bronchovascular structures. After

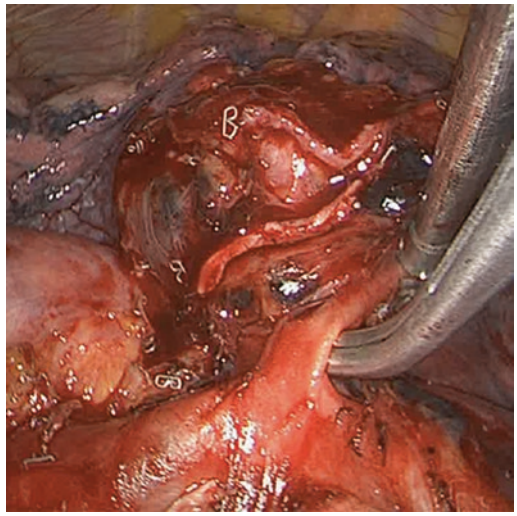

Fig. 5 Dissection of the lingular artery

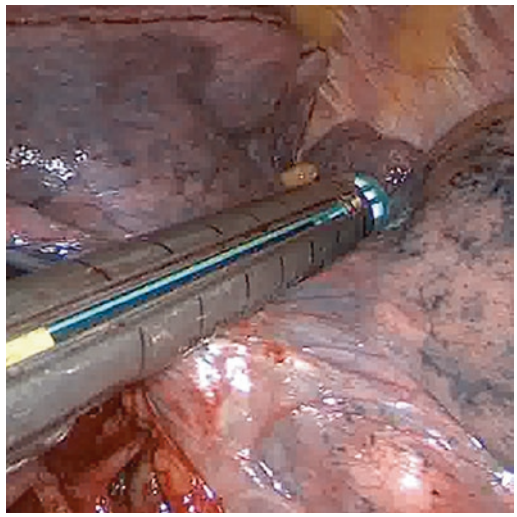

Fig. 6 Division of the fissure by stapler

identification of the upper and lower vein, the nodes at position 11 are removed, so the PA in revealed; the anvil of a 45-mm or 60-mm stapler is placed with the tip between artery and parenchyma, which is pulled into the stapler. The dissection is continued over the main PA until the fissure is completely transected; the "exit" of the tunnel is located between the artery of the posterior segment of the upper lobe (A2) and the artery of the apical part (A6) [5]. Removal of the specimen is performed using an endobag, to avoid contamination from a tumour. Usually, a single 24F or 28F chest tube is left in the chest for post-operative drainage of fluid and air.

Key Points

I. Clearly identification of the upper and lower vein before dissection.
II. In case of an incomplete fissure, opening the posterior pleura just above the superior segment artery may help to open the parenchyma. An alternative "fissureless technique" to prevent postoperative air leak, is to create a tunnel between the arterial plane and the lung fissure, which is divided with staplers. It also helps to detect anatomical variations and to reduce the risk of inadvertent transections.
III. Posterior PA branches can be multiple (from two to seven) may arise in random order; arterial branches are often small and short, and they may be divided using an endoscopic clips applier (click aV, GrenaR), two proximal clips and distal energy device.
IV. By careful during isolation of the upper lobe bronchus to avoid injuries of the interlobar PA. The right-angle clamp must be kept in contact with the airway to prevent any arterial damages.
V. Care must be taken during isolation of the small dorsal arterial branches after the upper lobe bronchus division; excessive traction may avulse these branches with significant bleeding.

Left Lower Lobectomy

After dissecting the ligament, the mediastinal pleura in opened anteriorly and posteriorly, so the inferior pulmonary vein can be readily isolated and transected with a vascular stapler (Fig. 7). The superior segmental vein can arise from a more cephalic position, so it is essential to make sure that this branch is included in the stapler.

In case of incomplete fissure or lymphadenopathy over the arterial plane, it's useful to isolate the lower lobe bronchus first with a bottom

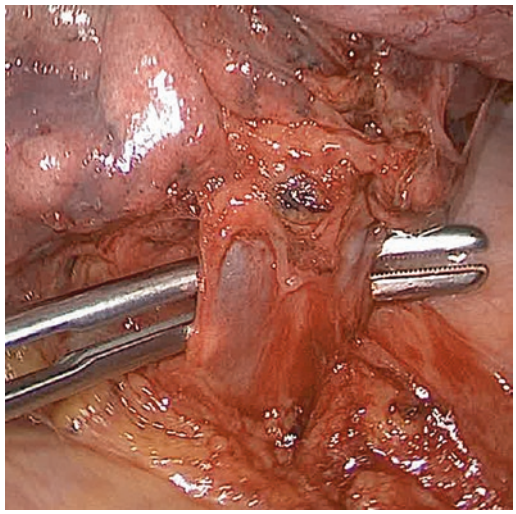

Fig. 7 Dissection of lower vein

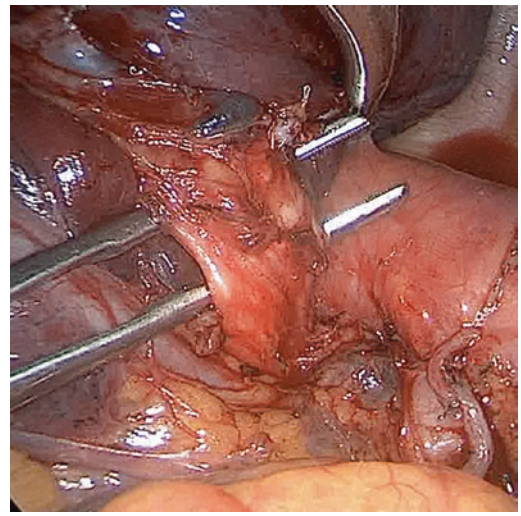

Fig. 8 Dissection of the lower lobe bronchus

to top technique (fissure-last). The lower lobe is pulled upward and tower the diaphragm, allowing better visualisation of the bronchus, which can be easily encircled and transected by 60-mm stapler (Fig. 8). The lung is now pulled back so that the artery can be appropriately identified; a blunt dissection of the sub-adventitial plane is then performed and the arterial branches to the basal pyramid and the branch for the upper segment of the lower lobe (A6) are clearly exposed (Fig. 9). The artery is now divided using a 30–45-mm vascular stapler. In the end, the oblique fissure in transected by 60-mm stapler, in a front to back direction.

If the fissure is complete, the left artery is easily recognised and isolated; the interlobar nodes should be removed, allowing better visualisation of the anterior part of the basilar artery. The anterior aspect of the oblique fissure is then opened, and the artery is divided by a vascular stapler; care must be taken to comprehend the A6 branch. The lower lobe vein is dissected and separated as described above after releasing the pulmonary ligament. The lobe is pulled laterally and posteriorly, so the lower lobe bronchus can be readily isolated and transected by a stapler, after testing inflation of the upper portion. The specimen in removed from the thoracic cavity

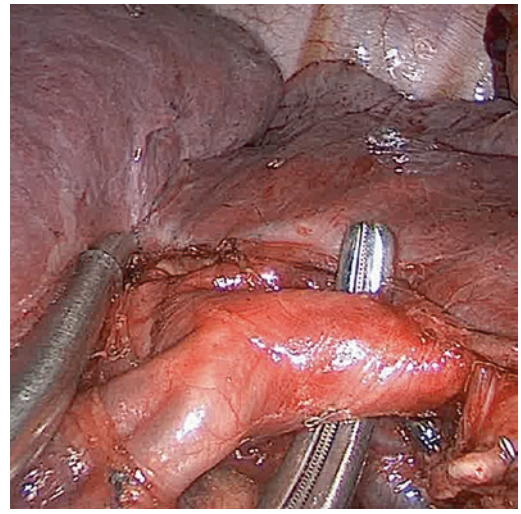

Fig. 9 Identification of the basilar artery

in a protective specimen bag to avoid tumor implantation in the incision and to minimise injury to the specimen.

Key Points

I. It is helpful to open the mediastinal pleura anteriorly to identify the upper lobe vein to confirm the presence of normal venous anatomy.

II. In the case of fissure-last technique (ligament, vein, bronchus, artery and then fissure), care must be taken not to damage the arterial basal branches to basal pyramid and A6 during the lower lobe bronchus isolation, that run close behind the airway. The clamp must be kept in contact with the posterior wall of the bronchus to avoid arterial bleeding.
III. A6 commonly arise as a single branch from the interlobar PA, but two or more separated branches can be seen. Sometimes the superior segmental artery can be originated more proximal and could be transected separately from the arterial basal branches. A6 occasionally rises from the lingular artery.
IV. The division of A6 can be made with a vascular stapler or using an endoscopic clips applier (click aV, GrenaR), two proximal clips and distal energy device (Fig. 10).
V. Care must be taken to avoid bleeding or occlusion of the branches destined for the upper lobe, especially the lingular artery when using the fissure-last technique.
VI. A lingular vein that drains to the left lower lobe vain in a rare anatomical variant, so attention must be taken during vascular transection (Fig. 11).

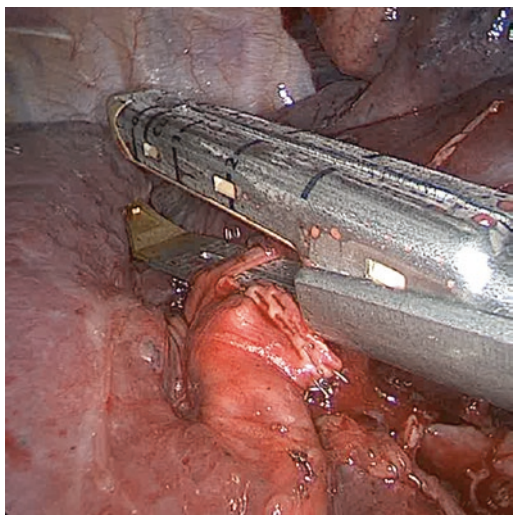

Fig. 10 Division of A6

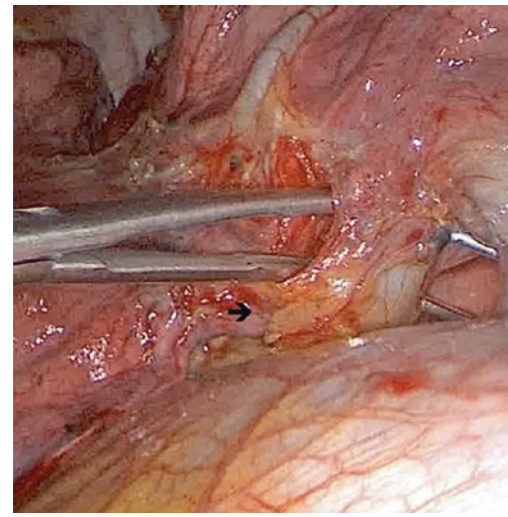

Fig. 11 Identification of the lower lobe vein (abnormal lingular vein, **dark arrow**)

Left Pneumonectomy

Video-assisted thoracoscopic pneumonectomy for lung cancer is still a relatively unusual procedure compared to other lung resections; however, the enhancement of the surgical instruments and advance in high definition camera has enabled to develop this approach. Pneumonectomy it is indicated when a lung-sparing procedure does not offer a complete resection. The indications of pneumonectomy are: central tumours affecting the main bronchus and/or central vascular structures; a tumour invading the fissure that affects the majority of upper and lower lobes simultaneously; the presence of positive interlobar lymph node(s) which infiltrate the main bronchus or the main artery and lesser resections are not amenable; two single and independent lesions in upper and lower lobes.

Under single-lung anaesthesia, a patient was placed in the lateral decubitus position. To perform a thoracoscopic left pneumonectomy, a 4–5 cm muscle-sparring utility incision is usually made in the anterior axillary line in the 4th intercostal space; the 10 mm, 30-degree thoracoscope in introduced in the 7th–8th intercostal space, in

the midaxillary line (biportal approach). For uniportal technique, though, the camera is placed in the upper part of the incision. After dissecting the pulmonary ligament, the anterior mediastinal pleura is fully opened, so to identify the upper and the lower lobe vein. To avoid pulmonary congestion, it is recommended to delay veins division. Hilum dissection proceeds upward around the pulmonary artery extending the dissection posteriorly to facilitate the dissection of the main pulmonary artery that is performed by blunt dissection in a sub-adventitial plane. Now, the upper lobe vein and lower lobe vein are divided by a vascular stapler. A rubber catheter looped around the central PA could be useful as a guide to safely bring the vascular stapler across the artery. To identify any hemodynamic instability of the patient during the procedure, it suggests keeping the stapler closed for a while before firing. Once the artery is taken, the main left bronchus should be dissected as proximal as possible to achieve a short stump and reduce the risk of postoperative bronchopleural fistula. The lobe should be retracted towards the apex and slightly anteriorly to enlarge the pathway to advance the stapler safely and near the carina. The stapler can be introduced from the utility incision in case of Uniportal approach or from the basal thoracoscopic port in the example of the biportal technique. Usually, on the left side, the bronchial stump retracts within the mediastinum, where the aortic arch works as natural protection. Dissection of 4L, 5, 6, 7, 8 and 9 groups are now performed.

Key Points

I. In contrast to right pneumonectomy, the risk for postoperative respiratory failure with left pneumonectomy is less.
II. Intrapericardial isolation of the main PA and/or of the veins is mandatory to gain proximal control safely in the presence of severe lymphadenopathy or case of a very short arterial trunk.
III. Protection of the bronchial stump could be performed using an intercostal muscle of the sale intercostal space of incision, thymic or pericardial flap or pleural flap.
IV. Cut the main bronchus close to the carina to get a shot stump and reduce the risk of postoperative bronchopleural fistula.
V. Attention must be taken to prevent damage of recurrent laryngeal nerve into the aortopulmonary window.
VI. Clear identification of the target structures is essential to avoid any damage to the surrounding structures during transection with endostaplers.
VII. Published series indicates that VATS left pneumonectomy is a safe and effective treatment procedure, with lower morbidity among selected patients with advanced malignant disease [6]; the benefits include less acute and chronic postoperative pain, shorter duration of intensive care unit/hospital stay and at least equivalent oncologic early outcomes, morbidity and mortality rates compared to thoracotomy [7]. However, more studies with longer follow-up are still necessary to clarify the benefits and the role of VATS pneumonectomy.

Left Sleeve Pulmonary Resections

Sleeve lobectomy should be indicated whenever possible for the treatment of centrally located lung cancer involving the pulmonary artery, the main or lobar bronchus, like carcinoid tumours; the procedure is a reasonable alternative to pneumonectomy as better preservation of pulmonary function and oncological safety. Although this approach is technically challenging, recent improvements in thoracoscopy and experience gained during VATS procedures have demonstrated that sleeve VATS lobectomy can be safely performed with good postoperative outcome.

Most surgeons in Europe, the USA and Japan use a 3–4 incision VATS technique, making a 5-cm utility incision at the 3rd or 4th intercostal space, in the midaxillary line [8]. Due to technical advantages in thoracoscopic instrumentation and experience gained from treating a large number of patients, some authors suggest that even complicated procedure like arterial sleeve or double sleeve, can be performed trough uniportal

approach; the camera is kept on the posterior part of the utility incision, the instrumentations are below the camera, in order to have a direct view with the surgeon's eyes above the hands [9].

Simple Bronchoplasty

When a tumour is located to the main bronchial base, the bronchus is cut in its origins by using a scalpel; now the suture can be easily made using monofilament absorbable continuous suture (PDS 3/0), with knots placed externally. Usually, flap protection is not needed.

Wedge Bronchoplasty

This is the case where bronchial resection must be more profound in a wedge shape to the main bronchus. The suture technique is the same as described above. To avoid excessive traction during bronchoplasty, it is helpful to perform a lymph node dissection of station seven.

Left Upper Sleeve Lobectomy

Bronchial anastomosis on the left side is more complicated than the same procedure on the right side, because of the absence of the intermediate bronchus, the main pulmonary artery, the short length of the upper bronchus and the presence of the aortic arch. The procedure is described as below.

After dissecting the pulmonary ligament, the anterior pleura is opened widely, so the upper pulmonary vein is easily visualised and transected by the vascular stapler. Dissection proceeds are opening the fissure to identification the pulmonary artery and its lobar branches; these are now divided separately by using an endoscopic linear stapler or an endoscopic clips applier. The interlobar and mediastinal lymph nodes should be removed, allowing better visualisation of the airway. Now, the bronchus of the target lobe can be dived with a long handle (No 10) with at least 0.5 cm proximal margin (sleeve resection). The specimen is then removed through the utility incision into an endobag. After evaluation of the bronchial stump by frozen section to be pathologically free of neoplasm, an end-to-end anastomosis can be performed.

Many authors choose an interrupted absorbable suture of 3/0 (Vicryl or PDS, Ethicon Inc., Somerville, NJ, USA), starting from the cartilaginous portion of the bronchial orifices, progressing on the membranous parts. Both sutures are then tied using a thoracoscopic knot pusher. They are tied with the knots outside to alleviate tension [10].

Diego et al. described the first report of a left-sided sleeve lobectomy by uniportal approach in 2013; the author suggests making a whole anastomosis using continuous absorbable suture (PDS 3/0); the stitching starts from the posterior wall of the bronchus, the anterior part is sewn, at last, both sutures are tied together [11]. The uniportal approach allows the target tissue to be directly visualised at the similar angle of view as for open surgery [12].

Another technique involves a running absorbable suture (3/0) reinforced with three-point interrupted suturing, as described by Han Y et al.; this method can secure the strength as well as saving the operation time [13].

Left Lower Sleeve Lobectomy

Only a few cases of left lower sleeve lobectomy with a thoracoscopic anastomosis are reported in the literature; the procedure is technically more complicated because of the presence of the main PA, which should be retracted during the process, the upper lobe vein and the atrium. Additionally, the main bronchus is usually located more deeply. Diego et al. suggest starting the end-to-end anastomosis, beginning with simple interrupted 3/0 absorbable suture in the cartilaginous-membranous junction, to approximating the main bronchus and the upper lobe; thus, will minimise anastomotic tension. Now, the posterior portion of the anastomosis is sutured with simple interrupted suture, from cranial to caudal; a 3/0 absorbable suture is then placed in the angle of the anterior wall of the bronchial cartilage, so thoracoscopic knot-pusher ties both stitches. The membranous portion is sutured in a continuous absorbable suture, from caudal to cranial; the remaining cartilaginous bronchus is sutured with 3/0 interrupted suture [14].

Artery Sleeve Resection

A tumour may invade the wall of the pulmonary artery or involve the origin of a sizeable lobar branch. In this situation, it is advisable to perform a combined sleeve resection or patch angioplasty of the pulmonary artery. Usually, this intervention is implemented on the left side because due to the close anatomical relationship of the left upper lobe with the mediastinal branches of the left pulmonary artery. The arterial sleeve resection is typically done after the bronchial anastomosis has been completed to avoid excessive retraction and handling of the vascular anastomosis; additionally, the transected artery allows excellent exposure for the bronchial anastomosis.

5000 UI of heparin sodium iv must be injected before clamping the pulmonary artery, to prevent thrombosis. Authors suggest using a thoracoscopic clamp, like D'Amico Clamp (Scanlan International, Inc.) for clamping the main PA; a tourniquet system may be used for PA clamping without interference the instruments through the utility-incision. For distal clamping, a bulldog clamp or a double vessel loop is useful for occluding the basal trunk of the pulmonary artery or the inferior pulmonary vein.

The extension of the PA reconstruction depends on the area of the artery involvement. If a tumour involves the base of one of the mediastinal branches without extensive involvement of the main PA, a tangential resection of the pulmonary artery followed by a direct arterioplasty with a running suture with 5/0 monofilament nonabsorbable material (Prolene) may be indicated. The clamp on the pulmonary vein (backflow) is now opened for de-airing; the proximal clamp is progressively released.

End-To-End anastomosis of the pulmonary artery is a difficult VATS procedure, which requires unique ability and significant experience in thoracoscopic procedures. The vascular sleeve is performed as the last step of the lobectomy, to avoid excessive traction on the pulmonary artery and to have a good exposure during the reconstruction. The suture of the PA is also tricky since the tissue is fragile.

A 5.0 or 6.0 non-resorbable monofilament suture with two needles is used for the arterial anastomosis; oxidised regenerated cellulose (Surgicel) may be used to cover the anastomosis.

Diego et al. suggest performing a running 360-degree suture starting from the posterior wall and finishing in the anterior wall [15]. The distal clamp is released before the knot is tied to fill the artery with blood backflow; the proximal clamp must be released gradually, so to visualise any bleeding between the suture that would require another stitch before removing the clamp.

Key Points

I. The management of the instruments and experience acquired in sutures is more critical in VATS than in an open thoracotomy; it is essential to keep tension and tie the interrupted sutures once they are placed.
II. The placement of the utility incision through the fifth intercostal space in a more lateral position than for traditional VATS (posterior axillary line) may be helpful during thoracoscopic bronchoplasty; the anastomosis can be completed in a manner like the conventional approach in anterior thoracotomy.
III. For left lower sleeve anastomosis, the posterior bronchial wall is thick and difficult to access, making it the most challenging part of the surgery.
IV. It is advisable to release the pulmonary ligament as well as the subcarinal lymph node dissection before the bronchial sleeve procedure to facilitate the lung mobility and to avoid traction on or manipulation of the anastomosis.
V. It suggests using a right-side double-lumen tube to reduce the bronchus tension.

Conclusions/Summary

VATS pulmonary resection has developed into a safe and effective treatment for lung cancer. With VATS techniques, major pulmonary resections can be performed with comparable

stage-specific 5-years survival as thoracotomy, with improved morbidity, reduction of acute and chronic pain, and loss of pulmonary function.

Prolonged air leak (PAL) is a common postoperative complication following pulmonary resections with prolonged LOS and more complicated postoperative course. Fissureless fissure-last VATS lobectomy is a feasible technique and appears to be a superior approach to conventional VATS lobectomy in terms of preventing PAL and reducing the hospital stay.

Self-study

1. VATS pneumonectomy is indicated in case of:
   (a) Central tumors affecting the main bronchus and/or central vascular structures—CORRECT.
   (b) Single lesion in upper lobe.
   (c) The presence of positive mediastinal (station 5) lymph node.
   (d) All of the above.
2. During a VATS left lower lobectomy with fissure-last technique:
   (a) The sequence of structure transection is: ligament, vein, bronchus, artery and then fissure.
   (b) During the dissection of the lower bronchus, the clamp must be kept in contact with the posterior wall of the bronchus to avoid any damage of the arterial basal branches to basal pyramid and A6; the artery runs close behind the airway.
   (c) The division of A6 can be made with a vascular stapler or using an endoscopic clips applier (click aV, GrenaR), two proximal clips and distal energy device.
   (d) All of the above—CORRECT.
3. The "tunnel technique":
   (a) Minimises the chance of post-operative air leaks.
   (b) The tip of the stapler should be placed between artery and parenchyma; it is important to keep the stapler steady and pull the parenchyma into the stapler. The ideal dissection plane in close to the artery.
   (c) It allows surgeon to open an incomplete fissure with staplers before bronchovascular structures are divided.
   (d) All of the above—CORRECT.

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Minimally Invasive Thoracoscopic Surgery—Anatomical Segment Resections

Brianda Ripoll, Sara Volpi, and Giuseppe Aresu

Key Points

Segmentectomies are bein performed with increasing frequency. In selected cases, segmentectomy seems to provide the same or better survival rates as a lobectomy, with the same mobidity and mortality and with greater preservation of pulmonary function. Compared to open precudes, a VATS segmentectomy can be performed safely and should be in the armamentarium of a thoracic surgeon.

Introduction

Segmentectomy is an anatomical pulmonary resection of one or more than one lung segments.

The first segmentectomy, a lingulectomy, was performed by Churchill and Belsey in 1939 for the treatment of bronchiectasis [1].

In 1940, after the dissection of 83 cadaveric lungs, Blades and Kent were the first to apply individual ligation and suturing to lobectomy, previously recommended only for total pneumonectomy [2]. During the 40s and 50s, most of the technical difficulties of lobectomy and pulmonary resection were overtaken and the principle of lung tissue conservation was developed. In 1947, Overholt and Langer pushed forward the idea of the bronchopulmonary segment as the primary unit, developing the concept of the intersegmental plane division as a 'precise, relatively avascular, and not traumatic' technique of lung parenchymal division [3].

Even though total pneumonectomy was still considered the only appropriate surgical option for the cure of primary lung cancer, over the following decades segmentectomy was increasingly applied also to the surgical treatment of small primary lung cancers in patients considered not fit for pneumonectomy [4, 5]. The use of segmental resections for the treatment of non-small cell lung cancer has been supported by the low mortality outcomes published by Rasmussen in 1964 [6] and by Bronfils-Roberts and Claggett in 1972 [7]. These publications lead the development and the diffusion of segmentectomy that rapidly become a relatively common procedure for lung cancer treatment.

The nineties were characterised by a rapid developed and diffusion of the Video-Assisted Thoracic Surgery (VATS) techniques [8].

The first VATS operations were typically performed using a 3 or 4 ports approach for relatively easy procedures but the evolution of the surgical devices and the advancement of the surgical techniques rapidly allow an adoption of the minimally invasive approach for anatomical lung resections.

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In parallel with the increased experience in this field an important number of variations have come to light, especially regarding the number, the position and the size of the ports. Needlescopic, biportal and uniportal VATS have been introduced with the aim to reduce the invasiveness and the traumatic injury of the intercostal bundles and therefore to improve the outcome [9–11].

Lately, the subxiphoid approach has also been proposed as a less invasive alternative approach for segmentectomies with good post-operative outcomes [12–15].

Indications

Segmentectomies are usually indicated in early stage non-small cell lung cancer (NSCLS), limited inflammatory or infectious disease, metastasis or indeterminate pulmonary nodules especially if deeply located or difficult to palpate [16–18].

The role of segmentectomies in case of NSCLC has been investigated in a large randomized controlled trial performed in 1995 by the Lung Cancer Study Group that demonstrated that sublobar resections for NSCLC smaller than 3 cm resulted in increased rate of locoregional recurrences compared to lobectomy (8.6 vs. 2.2%) [19], a result which has also been observed in a later study examining the SEER database [20]. These results led to restrict segmentectomy for patients with marginal cardiopulmonary function and otherwise not fit for lobectomy.

However, after the publication of the above-mentioned results, several other studies shown that anatomic segmental techniques could achieve comparable rates of recurrence and survival for stage IA NSCLC [21].

In addition, the prognosis seems not equivalent for all segments. For instance, left upper lobe segmentectomies and superior segmentectomies of the lower lobes have significantly less regional recurrence ($p = 0.029$) and comparable prognosis to lobectomies. In contrast, segmentectomies in the right upper lobe and of basal segments showed significantly higher local recurrence ($p = 0.001$). The poorest prognosis has been associated to basal segmentectomies versus lower lobectomies ($p = 0.005$) [22]. Nevertheless, if a strict inclusion criterion is followed, current meta-analysis validated that segmentectomies produce similar survival compared to lobectomy for patients with stage I NSLC [23].

Considering the latest studies segmentectomy has been suggested as a feasible option to achieve complete (R0) resection, in addition with adequate surgical margins and systematic nodal staging, may be associated with reduced morbidity and mortality as compared with lobectomy [24].

Further literature should be written in patients with diffuse emphysema, however, in stage IA with this condition (ppoVEMS < 40%), lobectomy outweighed a double therapeutic role because of lung reduction, especially in upper lobectomies [25].

A retrospective matched cohort study of consecutively acquired data suggested that post-operative lung function was significantly more preserved after segmentectomy than after lobectomy ($P < 0.001$) [26]. This difference may benefit borderline lung function patient in terms of postoperative quality of life or patients who may need subsequent lung resection [27].

Current understanding of radical segmentectomy can be summarized as follows. Firstly, the indication for segmentectomy should be limited to T1 tumours ≤ 3 cm in diameter, and HRCT and PET-CT findings must be taken into consideration, particularly for T1b tumours. Whenever nodal involvement or an insufficient margin is confirmed intraoperatively, segmentectomy should be converted to lobectomy with complete nodal dissection. Secondly, radical (intentional) and compromising indications for segmentectomy must be independently discussed. The former is for low-risk patients who can tolerate lobectomy. Thirdly, segmentectomy is more valuable than wedge resection from an oncological perspective because it allows nodal dissection at the hilum. Thus, the decision of the most suitable procedure, such as whether or not

to intraoperatively convert to lobectomy, should consider precise staging and the lower rate of local recurrence resulting from sufficient surgical margins. Therefore, segmentectomy must be clearly separated from wedge resection amongst the categories of sublobar resection for lung cancer. Surgeons must become adept and master **segmentectomy** as a keynote procedure because small lung cancers are being detected with increasing frequency [28].

Contraindications

Relative contraindications of VATS segmentectomy are severe emphysema and interstitial pneumonia, which make the dissection of intersegmental plane challenging. Extensive adhesion because of prior surgeries or pulmonary infections may be a technical contraindication. Patients with an unclear bronchovascular anatomy of the targeted segment, particularly intersegmental veins, are also ineligible for anatomical segmentectomy.

Anatomy

Before 1950, segmentectomies were not a common practice between thoracic surgeons. There were fifteen different classification systems making very confusing the understanding of the nomenclature [29].

In 1949, an International Committee selected between the 5 more commonly used systems of anatomy and nomenclature, to create a new system simple and easily translatable into different languages, where each bronchopulmonary segment would receive a number, and the part of the lungs supplied by the segmental bronchus would be given the name of the segmental bronchus (Fig. 1) [30, 31].

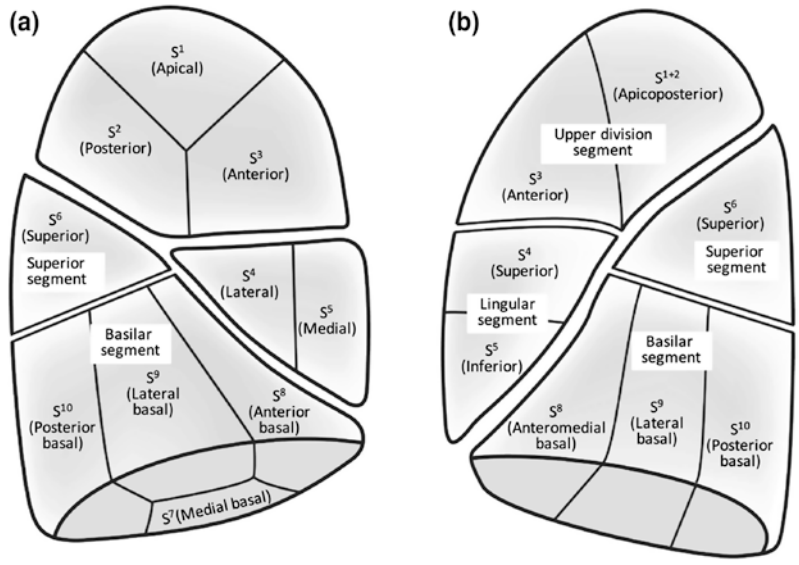

Fig. 1 Sealy WC (Mr) (1993). Naming the bronchopulmonary segments and the development of pulmonary surgery. Retrieved from Ann Thorac Surg.1993;55(1):184–8. An international agreement on bronchial nomenclature and anatomy was not reached until well after operations for bronchopulmonary segmental disease were well developed. R. C. Brock, in 1950, was the reporter of the efforts of The Thoracic Society of Great Britain to bring some order to this confused state. This Society delayed its action until an ad hoc committee made up of members from other countries and specialties met at the International Congress of Otorhinolaryngology in 1949. The anatomy and nomenclature of the bronchopulmonary segments was agreed upon. The Thoracic Society then accepted the report of the ad hoc committee

The requisite conditions for the presence of a lung segment are the following; each one of them has to be served by a constant individual bronchus, intersegmental sharp delimitation (must be sharply separated from one another) and have their base in the pleura and the top headed towards the hilum [32].

Nomenclature of the Segmental and Subsegmental Bronchi

The Right Lung

Right pulmonary bronchus divides in three bronchi: superior, middle and inferior.

The right upper lobe (RUL) bronchus originates 2 cm from the carina.

After the right upper lobe bronchus the right airway system continues as bronchus intermedius and approximately 1 cm after it bifurcates anteriorly to the right middle lobe (RML) bronchus and posteriorly to the bronchus of the apical segment of the right lower lobe (RLL).

Going into detail the segmentation of the lung is closely related with the bronchi (Fig. 2) [33].

Starting from the apical segment of the right lung, we can find the common root of anterior (B1) and posterior (B2) segments, known as Blsd. From this point, B1, subdivides in two segments, anterior (B1a) and posterior (B1b). The posterior bronchus (B2) originates in the lateral part of Blsd. Bronchus intermedius (BI) can be found immediately posterior to main right pulmonary artery and the interlobar pulmonary artery.

Further down the bronchus of the middle lobe extends in an anterior direction, with a slightly obliquus angle. The origin of the bronchus of the middle lobe also points out the origin of the superior bronchus of the inferior lobe (B6). It is possible at this level to see the trifurcation of the subsegments superior, medial and lateral. B6 is oriented vertically, medial and anterior to the pulmonary artery of the inferior lobe and it can be identified the bronchi B7, B8, B9 and B10.

The Left Lung

The Left Upper Lobe

The division of the bronchi is seen to split into two branches, one of which runs in a ventral direction and the other in a dorsal one. Sometimes the upper lobe bronchus divides directly into three, with a bronchus branch for each segment. In these cases, therefore, the anatomy is very simple.

The left main bronchus is longer than the right. 5 cm away from the carina, it passes under the aortic arch. At the secondary carina, it divides into the left upper lobe bronchus and the left lower lobe bronchus. This bifurcation is important for segmentectomy or lingulectomy, because the LUL bifurcates into the upper division (like the upper lobe in the right) and a trunk to the lingula (like the middle lobe). This allows to distinguish where to perform the resection whether an upper division segmentectomy or lingulectomy.

The left lung spreads from a common trunk at the anterior superior border of the Blsi. From here, the anterior bronchus (B3) is easily noticeable at the same level where B1 + 2 begins and it has an horizontal direction.

Blsi continues inferiorly with the BL which as an oblique direction, looking down and ahead.

Superior lingular bronchus (B4) runs horizontally and in this stage, it is possible to see B5 given that it runs adjacent to the left pulmonary artery.

Distally to the caudal progressive separation of BL and Blii, there is the common trunk of B7 + 8 and bronchi B9 and B10.

The Left Lower Lobe

The further division of the lower lobe is difficult to describe accurately due to anatomical variations.

It may be said that two large branches serve a dorsal-medial segment and a ventral-lateral segment. The further division of the ramifying branches varies. As a rule, there are four. The rest of the lower lobe consists of the areas served by the two large branches; the medial and the lateral, that can be regarded as segments.

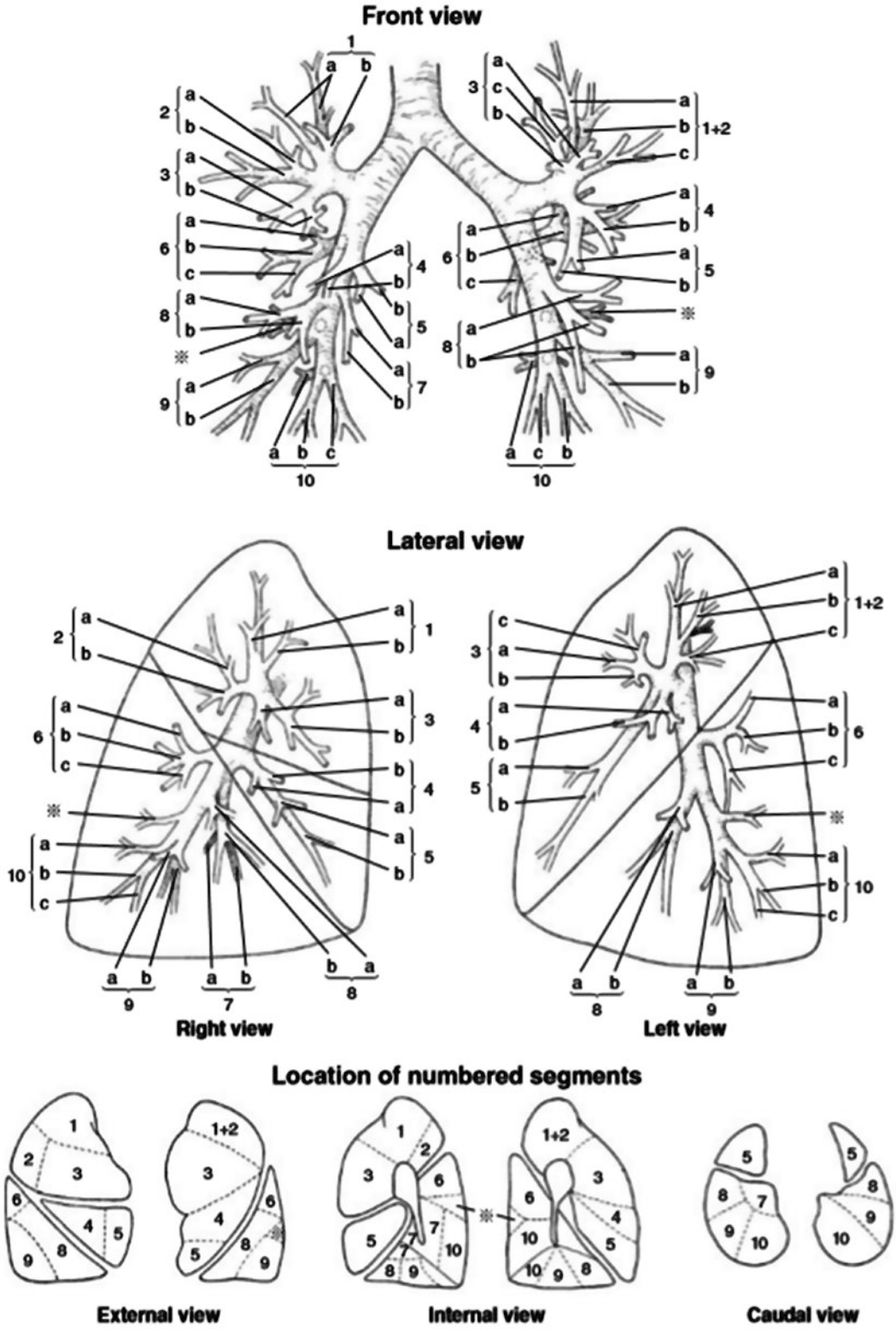

Fig. 2 Nomori, H; Okada, M (2011) ed. Illustrated Anatomical Segmentectomy for Lung Cancer. 1st ed. Springer, Page 6, Fig. 1. A nomenclature of the pulmonary segments with the bronchus

Nomenclature of Segmental and Subsegmental Arteries

All the arterial branches are named with the number corresponding to the bronchial and the lung segment. It is important to introduce here the concept that each segment has a subsegment.

Most of the segments are divided in two, denominated "a" and "b", and some of them they have got 3 subsegments, "a", "b", and "c". This applies to the left upper lobe, the S6 both side, and S10 (Fig. 3).

The arterial and venous division follows this subsegmentation, and that is reason why lower lobes segments, are technically more difficult.

A nomenclature of the pulmonary arteries respecting the distance from the right ventricle is widely used as follows: first order branch, the pulmonary trunk; second order, the left and right main pulmonary arteries; third order, the upper and lower trunks and "lobar" arteries; fourth order, all 10 segmental arteries; fifth order, subsegmental arteries arising directly from a segmental artery; sixth order, arteries arising directly from the first division of a subsegmental artery; and so on.

The Right Lung

1. Right upper lobe

The right pulmonary artery arises from behind the superior vena cava, from this point gives an anterior trunk to the upper lobe. The rest of the artery descends to supply the lower and middle lobes behind the superior pulmonary vein, thereby it is a danger point during surgeries when it is required to encircle that structure.

In the angle between the lower border of the upper lobe bronchus and bronchus intermedius, it can be found the major fissure sitting behind the 11 lymph node station. This point is key to understand the irrigation of the posterior segment of the upper lobe, because it is the place to access to the ascending pulmonary branch, which supplies this part of the lung.

2. Right middle lobe and Right lower lobe

Following the major fissure, the pulmonary artery trunk divides in two. One branch goes to the middle lobe, and opposite that another branch goes to the apical segment of the lower lobe (Table 1).

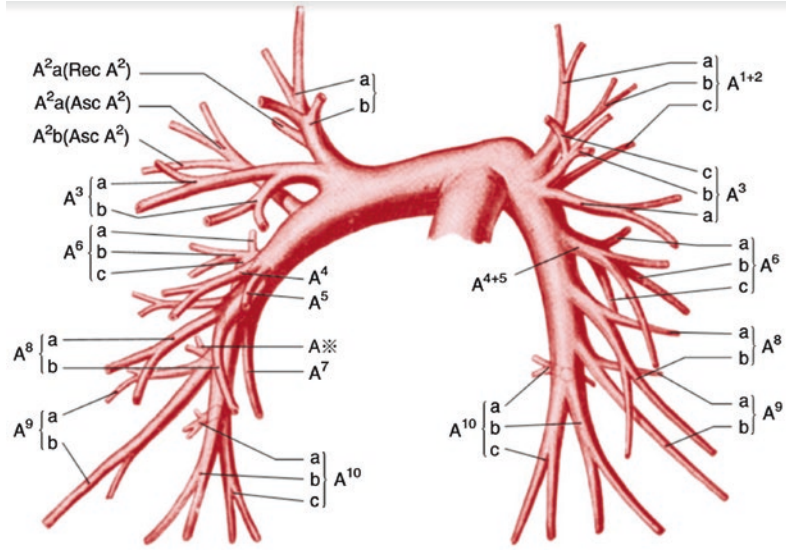

Fig. 3 Nomori, H; Okada, M (2011) ed. Illustrated Anatomical Segmentectomy for Lung Cancer. 1st ed. Springer, Page 6, Fig. 1. A nomenclature of the pulmonary segments with the bronchus

Table 1 Segmental and subsegmental arteries of the lungs. Arteries underlined have 3 subsegmental arteries

Right lung			Left lung		
Upper	A1	A1 a & b	Upper Division	A1 + 2 A3	A1 + 2 a & b & c A3 a & b & c
	A2	A2 a & b			
	A3	A3 a & b			
Middle	A4	A4 a & b	Lower (lingular)	A4	A4 a & b
			Division	A5	A5 a & b
Lower	A6	A6 a & b & c	Lower	A6	A6 a & b & c
	A7	A7 a & b & c			
	A8	A8 a & b & c		A8	A8 a & b
	A9	A9 a & b & c		A9	A9 a & b
	A10	A10 a & b & c		A10	A10 a & b & c

The Left Lung

1. The left upper lobe

The left pulmonary artery emerges beneath the left pulmonary artery beneath the aortic arch and arches over the left main bronchus. It then enters the fissure from its posterior aspect, giving a short, wide, anterior trunk.

The segmental branches of the left pulmonary artery comprehend the posterior segment of the left upper lobe, lingula, apical segment of the left lower lobe, and basal segments (Table 1).

The final branch supplying of the lingula is made of a variable number of posterior segmental arteries from the left pulmonary artery.

Nomenclature of Segmental and Subsegmental Veins

The venous vasculature of the lung is known to be difficult to concrete due to its anatomical variation and lack of consensus in the literature. Most of them are not only divided in subsegmental veins, there is also the presence of intersegmental veins dividing the segments (Fig. 4). These intersegmental veins are key during dissection time, because they define the intersegmental plane and therefore the anatomical landmark.

There is a difference in the division of the veins between the right (Table 2) and the left side (Table 3). Again, every segment is subdivided in at least two subsegmental veins, however, there are segments that contain a third subsegmental vein, and also an intersegmental vein.

Surgical Technique

The essential concept about the approach to VATS segmentectomies is the extracorporeal performance of the entire operation, without direct visualization of the operative field. Every segmental structure (bronchus, artery, vein) is individually ligated.

The anatomical segmentectomies are technically very demanding for different reasons. Firstly, because of the anatomical variation between patients. Secondly, most of the nodules are non-palpable, and are usually located in the inner part of lobe and fissure, and in this area there is no clear landmarks.

Bronchoscopy is usually performed before the start of the surgery. Bronchoscopic findings are compared with the preoperative CT scan to help the surgeon to orient the shape and size of the lobe about to work in, and to localize the pattern and distribution of arterial and venous branches.

The high variability of the segmental anatomy explains the current trend towards the development of different preoperative advanced 3D reconstructions or models tailored for each patient [34].

The number of access ports usually ranges from 1 to 4 and includes an access window for the retrieval of the specimen.

The attempt to reduce the invasiveness of the procedure and the consequent intercostal nerve injuries has led to a reduction of the number or ports and the use of uniportal techniques is becoming more and more frequent.

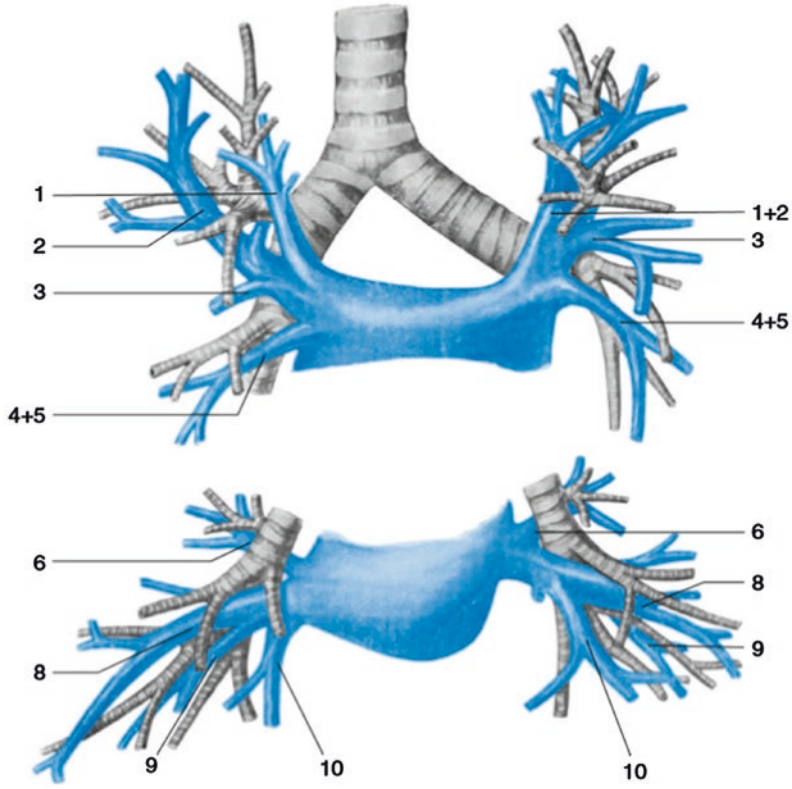

Fig. 4 Nomori, H; Okada, M (2011) ed. Illustrated Anatomical Segmentectomy for Lung Cancer. 1st ed. Springer, Page 22, Fig. 3. A nomenclature of the pulmonary veins respecting the distance to the bronchus

Table 2 Nomenclature of segmental and subsegmental veins of the right lung

The right lung					
Upper	V1	V1a: S1a & S1b V1b: Sib & S3b	Lower	V6	V6A: S6a & S6b + c V6b: S6b & c, S8 + 9
	V2	V2b: S2b & S3a V2b: S2b & S3a V2c: S2b & S3a V2t: below S2a		V7	V7a: S7a & S7b
	V3	V3a: S3a & S3b V3b: below S3b		V8	V8a: S8a & S8b V8b: S8b & S9b
				V9	V9a: S9a & S9b V9b: S9ab & S9b
Central vein		V2a + V2b + V2c (V3)			

To further avoid intercostal nerve damage, subxiphoid uniportal approaches have also been reported with good results.

However, reducing the number of ports may conversely increase the complexity of the procedure, and surgical outcomes may be affected by the ability of the operating surgeon.

The mediastinal and hilar lymph nodes should be at least sampled systematically because any lymph metastasis will require a formal lobectomy.

Table 3 Nomenclature of segmental and subsegmental veins of the left lung

The left lung					
Upper	V1 + 2	V1 + 2a: S1 & S3	Lower	V6	V6a: S6a & S6b + c V6b: S6b & S6c + S8, 9 V6c: S6c & S10a & S7
		V1 + 2b: S1 + 2a & S1 + 2b V1 + 2c: S1 + 2b & S1 + 2c V1 + 2d: S1 + 2c & S3a		V8	V8a: S8a & S8b V8b: S8b & S9b
	V3	V3a: S3a & S3b V3b: S3b & S4b V3c: S3b & S3c V2a + V2b + V2c (+V3a)		V9	V9a: S9a & S9b V9b: S9b & S10b

Another challenging step of the process is the correct differentiation of the intersegmental plane, which is achieved by selective and differential inflation of the segments, where the fissures between each segment can help the surgeon to differentiate.

A combination of infrared imaging and injection of ICG can be used to identify the intersegmental plane. In contrast to intravenous injection, the transbronchial injection of dyes allows the identification of the intersegmental plane not only at the lung surface but also within the parenchyma.

Once the intersegmental plane is marked, is fixed by a stapling device to create a fissure.

Postoperative Complications

Despite the technical complexity of VATS segmentectomies there is a low reported conversion rate, (Shiraishi 0% [35], Atkins 0% [36], Oizumi 0% [37], Watanabe 0% [38], Yamashita 4.8% [39].

The reported complication rate is variable on the different reports (Shiraishi 11.7%, Atkins 31.3%, Oizumi 10%, Watanabe 10%, Yamashita 19% Okada 13.5%, Schubert 26% [40]).

There are many specific complications, mainly vascular complications and haemorrhagic, followed by bronchial complications. Another reported complication is torsion and venous ischemia [41] due the mobility of the remaining segments that might require anchoring [42].

Regarding the intersegmental plane, we may have staple line disruption, prolonged air leak (4.2%) [43] venous injury [44] and anatomical misjudgement [45].

Models to identify patients at increased risk of prolonged air leak using preoperative factors have been developed stating other types of preoperative risks such as Male gender ($p=0.08$), smoking history ($p=0.03$), body mass index (BMI) 25 or below ($p<0.01$), Medical Research Council (MRC) dyspnea score above 1 ($p=0.06$), and diffusion capacity for carbon monoxide below 80% (Dlco) ($p=0.01$) [44, 46].

Other pulmonary complications described are atelectasis and pneumonia, atrial fibrillation or supraventricular tachycardia, empyema and haemothorax [47].

Conclusion

Although VATS segmentectomy has gradually gained popularity, its oncological indication in lung cancer remains a matter of debate, and the validation of long-term outcomes is required. Nonetheless, considering the latest studies and technical evolutions, VATS segmentectomies may become more and more indicated and therefore should be among the surgical options offered by thoracic surgeons when required.

Self-study

Question 1: Regarding the anatomy of the lung, which one of the following statements is true:

a. The normal anatomy of the bronchae does not interfere in the localization of the injuries per aspiration.
b. The lung's division in segments does not have any application in Radiology.
c. The lung's division in segments does not have any practical application in Surgery.
d. The main right bronchae is narrower than the left one.
e. The main bronchi follow the pulmonary arteries at the hila.

Answer: e.

Question 2: Regarding segmentectomies, which of the following statements is false:

a. Segmentectomy is an option for small, anatomically well situated lung cancer.
b. In lung cancer resection, as long as the removal of the segment contains the malignant tissue from a lobe that lobe, the mediastinal lymph node resection (right and left sided) is not required.
c. Patients undergoing VATS segmentectomy had significantly reduced chest tube durations and hospital stays.
d. Segmentectomy can be performed for secondary lung cancer.
e. The creation of a segmental fissure and dissecting out the segmental vessels can be done using a thoracoscopic technique.

Answer: b.

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Subxiphoid Approach for Anatomical Lung Resections and Lobectomies

Daniel R. Sitaranjan, Haisam Saad, Jiang Lei, and Giuseppe Aresu

Key Points

1. Resectability of the tumour and operability of the patient should be assessed using an MDT team approach to treatment including; radiologist, surgeons, anaesthesiologists, respiratory physicians, oncologists and pathologists.
2. Adhere to the inclusion and exclusion criteria for SVATS lobectomy—particularly at the beginning of SVATS experience.
3. Case selection initially should be wary of lower lobe tumours and posteriorly positioned masses, particularly in the left hemithorax, as access can be more complex.
4. Correct positioning and instrumentation is paramount for safe technically feasible procedure.

Introduction

Thoracic surgery has been an ever-evolving specialty with constant refinement and introduction of new techniques and technologies. The era of video assisted thoracic surgery has blossomed from multi portal approaches to uni-portal techniques with subxiphoid being the most recent development in this ever-changing landscape.

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What has driven this development is the thoracic surgical community's commitment to improving patient centred care and alleviating morbidity thereby inferring a better quality of life to the patient post-operatively. In 1995 the treatment guidelines of the American Society of Clinical Oncology considered an improvement in quality of life to be a necessary objective in justifying the recommendation of new therapeutic strategies.

Video-assisted thoracoscopic surgery started in the early twentieth century and in 1992 the first anatomical lung resection for malignancy was described by Roviaro et al., performed using four ports and a 4 cm utility incision. The introduction of video assisted thoracoscopic surgery from open procedure has certainly achieved comparable oncological results with reduced trauma, less chronic pain, quicker discharge and improvement of several post operative quality of life determinants. A review published by Coffey et al. indicate that even more favorable oncological outcomes are achievable with VATS and an earlier access to adjuvant chemotherapy could be offered due to the faster post operative recovery. A randomized control trial published in the Lancet in 2016 by Bendien et al. confirmed that VATS is associated to less postoperative pain and better quality of life than anterolateral thoracotomy for the first year after surgery, suggesting that VATS should be the preferred surgical approach for lobectomy in early stage non small cell lung cancers.

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Studies have also reported a lower acute phase inflammatory response, with a lower release of interleukins and C-reactive protein in minimally invasive procedures (Ref. Shanghai/Rivas). VATS resection for lung cancer also allows improved operability on those patients who are at high risk, for example, older patients and those with poor pulmonary function. A movement away from open techniques, where appropriate, has increased the cohort of patients who can safely undergo surgical management of their cancer (Fig. 1).

The uptake of the VATS lobectomy on the international stage can be seen in the figure adapted from Detterbeck et al. There has been rapid uptake of VATS technique in recent years and now a greater proportion of pulmonary resections are performed by VATS.

In 2010 the use of uniportal access was used for the first time to perform an anatomical lung resection. Similar to its predecessor single-incision VATS lobectomy follows the oncological principles of major pulmonary resections by VATS with individual dissection of veins, arteries, and bronchus. It also allows a complete mediastinal lymphadenectomy.

In traditional VATS surgery the instruments and the thoracoscope enter the thoracic cavity through intercostal ports which can cause nerve injury, acute and chronic pain and other neuropathic syndromes. This problem could also be not necessarily avoided with single incisions VATS surgery as you could potentially cause similar troubles due to instrumentation between the ribs.

With the aim to avoid the injury of the intercostal nerves the Subxiphoid thoracic surgery was introduced. In 2014 Liu et al. reported the first VATS lobectomy using a subxiphoid uniportal approach. Shanghai Pulmonary hospital has taken subxiphoid VATS surgery to the next level using this technique for a large number of lung resections including segmentectomies. This chapter aims to outline the considerations and operative technique of performing a subxiphoid VATS lobectomy.

Patient Selection

Correct patient selection is paramount to the success of any surgical practice. Preoperative assessment should be undertaken as usual for any other surgical case, alongside some extra SVATS specific considerations. Resectability of the tumour and operability of the patient should be assessed using an MDT team approach to treatment including; radiologist, surgeons, anaesthesiologists, respiratory physicians, oncologists and pathologists. Case selection criteria can be expanded depending on surgeon and centre experience in subxiphoid thoracic surgical procedures. In the initial stage, where teams are at the beginning of the learning curve, it is crucial to select patents carefully as outlined by the following list adapted from Abdellateef et al.

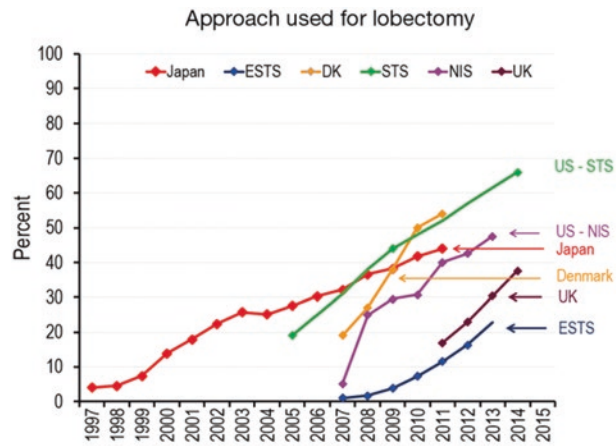

Fig. 1 This is a graphical representation of the proportion of lobectomies via VATS performed internationally from Detterbeck et al. 2016. Figures obtained from: US STS (United States Society of Thoracic Surgeons), US NIS (United Stations National Inpatient Sample), UK (United Kingdom, ESTS (European Society of Thoracic Surgeons)

Inclusion criteria:

- for major lung resection, it is advisable to include only cases with lesions of T1 or T2 status of tumour <7 cm for lobectomy and lesions <2 cm for segmentectomy;
- N0 status for tumour;
- localised infectious lung disease.

Exclusion criteria:

- central masses;
- enlarged lymph nodes with confirmed N1 or N2 disease;
- chest wall involvement;
- Re- do thoracic surgery;
- cardiomyopathy, impaired cardiac function, cardiomegaly;
- obese patients with body mass index >30 who may show difficulty in localisation of xiphoid process in addition to the abundant pericardial and pleural fat which makes access to pleural space more difficult and time consuming.

There are other important considerations in the SVATS approach to lobectomy. Posterior lesions require considerable traction in order to expose the relevant structures and distract the lung parenchyma. In the beginning of an SVATS programme, it would be advisable not to approach posterior masses which require synchronous wedge resection.

The subxiphoid approach is more challenging on the left side due to the cardiac pulsation with risk of intra-operative arrhythmia or contusion to the myocardium. Patients with significant cardiac history of arrhythmia, cardiomegaly, cardiac surgery etc. should be selected with care particularly if the lesions are left sided. As part of preoperative assessment the heart and its relations to surrounding structures should be observed along side a detailed preoperative echocardiogram and further cardiac testing if indicated.

Operation Set Up

Preparation of the patient for SVATS is key to success as positioning and ergonomics of your set up will aid in the pulmonary resection. One monitor is placed cranially above the head of the patient. The surgeon and the scrub nurse stand on either sides in cases where the patient is in a supine position or on the abdominal side if the patient is lying in the lateral decubitus position with the assistant standing opposite. A 10-mm, 30-degree angled high-definition video thoracoscope (Karl Storz, Tuttlingen, Germany) is used. Usual VATS instruments plus the dedicated instruments specially designed for SVATS are used during the operations.

Anaesthesia

All cases are performed under general anaesthesia and patients are intubated with a double lumen tube. At this point routine bronchoscopy can be undertaken prior to positioning of the patient. Single lung ventilation is conducted allowing collapse of the lung from where resection will take place.

Positioning of the Patients

Positioning of the patients will vary depending the laterality of the lesion and its site within the chest. In the case of bilateral lesions or concomitant mediastinal and pulmonary lesions, it's preferred to put the patient in the supine position with both upper limbs adducted beside the patient. In the case of synchronous lesions a 30° up tilting of the operated side may provide more space and improve the surgeons comfort during the operation. Further-still, use of a small roll between the scapular or even a sternal elevator will allow even more space during the operation. Some surgeons prefer to put small soft roll between the two scapula or use a sternal elevator to elevate the sternum to get more space during the procedure (Figs. 2 and 3).

In case of unilateral pulmonary lesion, the patient is placed in the lateral decubitus position

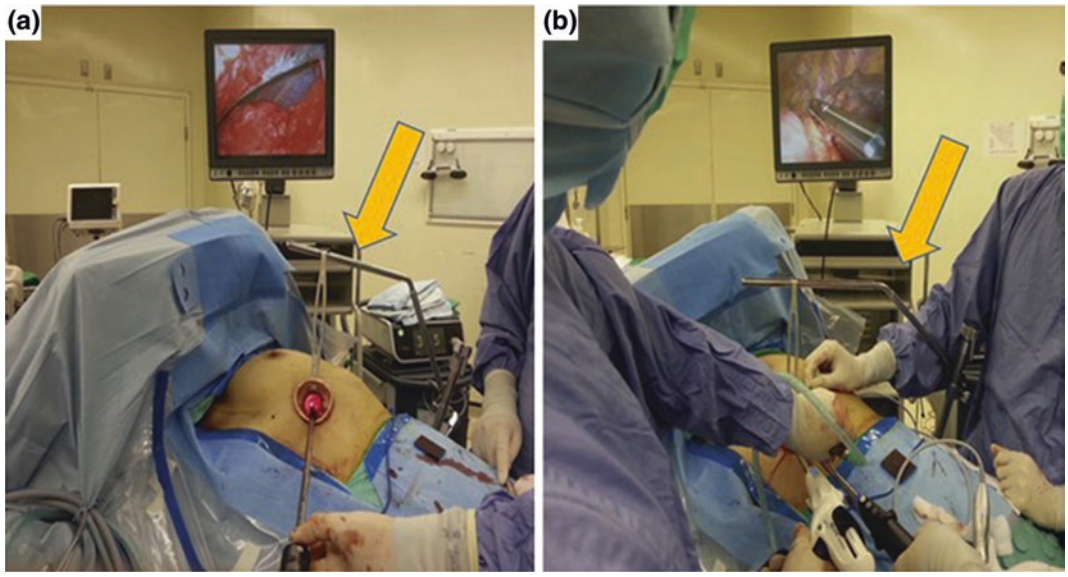

Fig. 2 A + B Patient positioned in lateral decubitus position with use of a sternal elevator (yellow arrow)

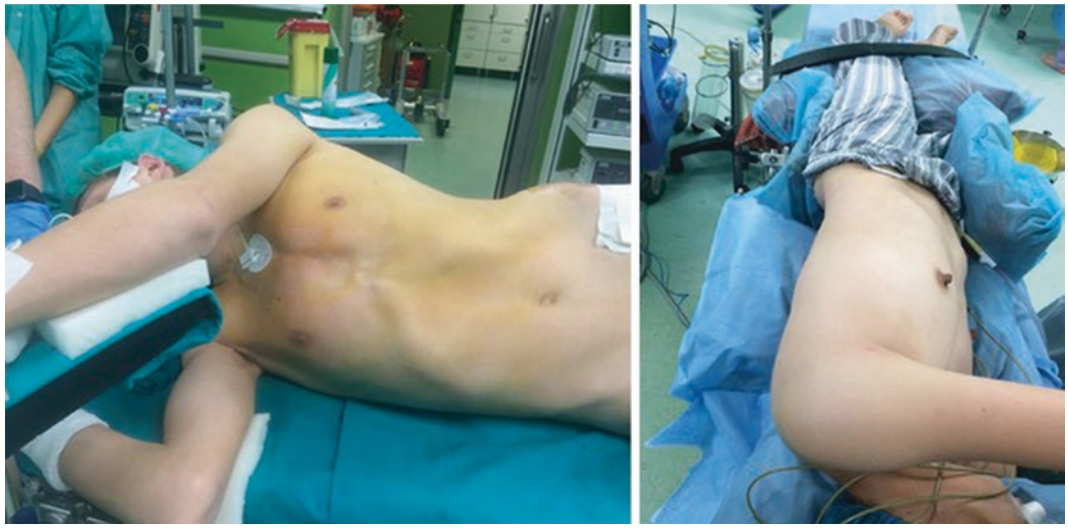

Fig. 3 Patient in lateral decubitus position with 30 degree backward inclination

with 30° backward inclination and the patient should be secured to the table to prevent a fall.

The supine position gives one access in case of bilateral or concomitant mediastinal and anterior pulmonary lesions but does not allow a good visualisation of the posterior part of the hilum.

A lateral decubitus position with a 30° posterior inclination is the preferred one in case of anatomical lung resections as helps to displace the lung posteriorly giving a clearer view of the hilum and giving more space for instruments with less interference between them and the heart. In this position exposure of the hilar and fissural structures come at ideal angles so when using the long curved tipped SVATS instruments dissection can be more purposeful and directly

into the spaces between the structures and anatomical landmarks can be freed more easily.

In the set up of these cases, the surgeon must always be prepared for the possibility of unpredicted challenges and complications such as significant bleeding e.g. pulmonary artery injury. In these situations conversion to a classic lateral VATS approach or thoracotomy should be straightforward. It is advisable to suspend the arms abducted from the body even when supine to free the lateral chest wall so that just rotating the table anteriorly it would be possible to get a traditional lateral decubitus position. Subxyhpoid lends it self to easy opening of the sternum via median sternotomy but this is more useful for SVATS thymectomy.

Instrumentation

Considering the peculiarities of SVATS, the implementation of dedicated instruments has been very important to make this approach easier and feasible for multiple procedures.

Special self-made instruments for SVATS have been manufactured by the Shanghai Medical Instruments Group Ltd., Shanghai, China, with the main aim to overcome the longer distance to the hilum and the different axis. The diagram below shows lung graspers, dissectors, stapler guider, electrocautery blades and others all of which share longer shafts, with a distal curved tip (Fig. 4).

Incision

A 3–5 cm longitudinal incision is made in the subxiphoid area. The incision is transverse at the level of xiphoid process extending between the 2 costal margins for bilateral procedures and longitudinal extending from the xiphisternal junction to 1 cm below the xiphoid process for unilateral procedures.

Then subcutaneous tissue and rectus abdominis are separated along the xiphoid process. The xiphoid process can either be preserved or completely resected to facilitate the access. Blunt dissection using one finger via the infra-sternal angle between the xiphoid process and the subcostal margin toward the operated side will create a retrosternal tunnel to open the required pleura. Creating the retrosternal tunnel can be visualised by insertion of the camera through the incision and carrying out the dissection using electrocautery. Once the required pleural is opened, a wound protector is inserted giving more space for the camera and instruments without the need of a sternal lifter. For bilateral procedures, a sternal retractor/lifter can be used, connected to the traction frame and placed under the sternum, which is elevated

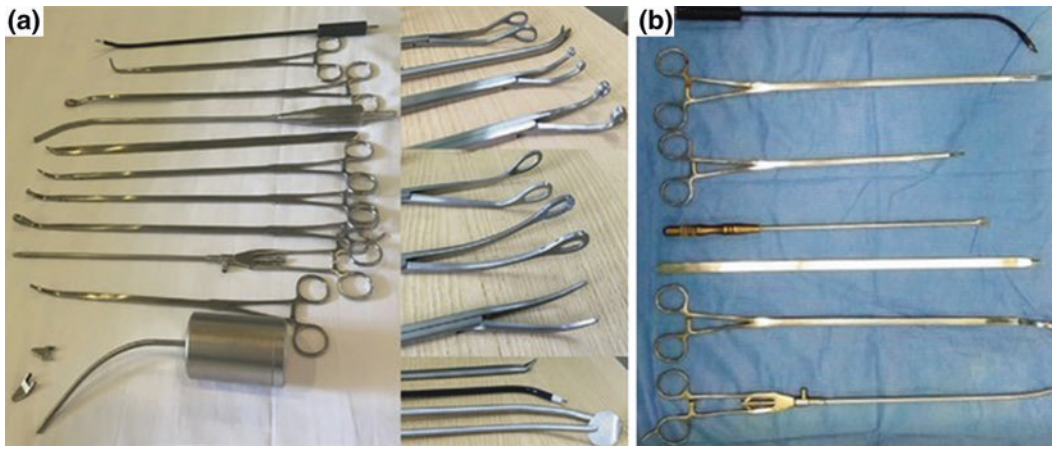

Fig. 4 Instruments designed for SVATS (Shanghai Medical Instruments Group)

to facilitate the access. If the pericardial fat tissue near or around the wound is obstructing the access, resecting it at the beginning of the surgery will improve it.

Lobectomy and Segmentectomy

The subxiphoid approach carries a number of advantages. The location of the incision which is at the level of fifth costal junction to the sternum with the instruments running parallel to the mediastinum, makes the oblique fissure in front with easier visualisation of inter-lobar structures. The anterior and apical pulmonary arteries plus the superior and inferior pulmonary veins are easily approachable anteriorly or inferiorly. This will also provide more convenient angles for the staplers. The subxiphoid approach is therefore considered convenient for performing both lobectomy and segmentectomy.

The limitation of subxiphoid approach is mainly when targeting the lower lobes due to the limited visual field which means the upper and middle lobes tend to be easier targets. The lower lobes are complicated by the proximity of the diaphragm and compression of the heart during left-sided operations and difficult access to posteriorly located lesions.

Surgical Steps

After entering the pleural cavity, the interlobar fissural status is assessed, upon which the approach towards the lobectomy is determined. The lung is retracted using specially designed long curved lung grasper held by the assistant and dissection is carried out by the surgeon using a suction instrument in their left hand and a long curved laparoscopic hook, electrocautery or 5 mm blunt tip LigaSure of 37 mm length in the right hand. Use of a long sucker with distal curvature can be beneficial to slightly retract the pericardium medially in order to optimise visualisation, being careful not to disturb the cardiac function or venous return.

The order of stapling the artery first, vein then bronchus is usually followed but it can change depending on the anatomical peculiarities of the patient. If the fissure is well developed, the surgeon should try to open it early to delineate the vascular anatomy, but if not well developed, the fissure could be left as the last step. Vessels, bronchus and fissures are exposed and divided with appropriate straight or articulated endostaplers. In some cases, a curved-tip stapler technology is used to facilitate the passage around the structures. To transect minor pulmonary arteries, usage of proximal and distal silk ligature or polymer clips then resection in between thermal device. A specimen pouch catch bag is used to remove the specimen, with prior removal of the wound protector.

Segmentectomy is now widely performed and even posterior segments (S2, S6, S9, and S10) that were thought to be inaccessible via SVATS are routinely performed by experience SVTAS surgeons. The key to SVATS segmentectomy is to master routing lung resection and case load before attempting segmentectomy. would not be accessible by SVATS.

In all indicated cases systemic lymph node dissection should be done according to the IASLC/mountain classification. Some lymph node stations can present difficulty to the accessing particularly the posteriorly located sub-carinal lymph nodes. Dissection of the posteriorly located sub-carinal lymph nodes can be performed but requires maintained anterior traction of the lung by a lung gasper held by the assistant along with simultaneous dissection by the surgeon. Tilting the patient more toward the lateral position while working posteriorly may facilitate more access to the posterior lesions and lymph nodes.

After completion of the procedure, the bronchial stump is checked under water for air leak. In the subxiphoid approach, it is difficult to flood the surgical field with water to test air leak by the usual manner as the wound through which you pour the water is lower than the surgical field and not as high as that of lateral approach leading to getting the water back out of the incision or inability to fill the surgical field adequately. That is why a special metal

pot with long nozzle was designed to deliver the water from outside the wound to deep inside the surgical field making that mission easy and feasible.

Wound Closure and Drainage

At the end of the procedure, a 28Fr pleural drainage tube is inserted at the inferior end of the incision passing laterally to the thoracic apex, and then connected to a drainage bottle. A deep venous puncture catheter may be inserted at the 8th intercostal space on the lateral chest wall then connected to a drainage bag as a basal drain. An additional drainage tube is inserted in the other end of the incision in patients with concomitant mediastinal lesion, bilateral lesions or associated opening of the pleura during thymectomy. Only one drain is inserted on one side of the incision in case of isolated mediastinal lesion. The incision is closed in layers. All patients are extubated on table (Fig. 5).

Outcomes

Subxiphoid pulmonary resection has great potential in providing a treatment that offers oncological resection alongside lymph node sampling whilst having low morbidity and improving patient quality of life by reducing post-operative pain. Despite these theoretical benefits, as with any new intervention, these advantages must be proven scientifically with well powered studies and trials. Published in the European journal of Cardiothoracic Surgery in 2016 Hernandez-Arenas et al. presented data on 153 SVATS cases whereby 105 had lobectomies and 48 had segmental resections. Notably mean operative time was 166 minutes and likely can be attributed to experience in a new technique and can be postulated that this will improve with experience The most common complication in 13% of the cases was preoperative arrhythmia and as discussed previously this is likely due to compression of the heart most common in left side cases. Comparably they had a post-operative mortality of zero at thirty days and R0 resection was achieved in all cases. The postoperative pain in this cohort of patients was that by day 7 at least 70% of patients were pain free.

Similar results have been presented in 2018 European Society of Thoracic Surgery where Jiang Lei et al. presented data confirming the benefit of reduced post-operative pain by SVATS approach. They randomised 1083 patients to VATS lobectomy and 808 to SVATS approach to lobectomy. The results were completely comparable with no benefit inferred to either group in most complications or mortality. VATS had a higher rate of wound infections. Most notably SVATS showed far superior pain scores at 1, 3, 6 month and over 1 year follow up on each occasion compared to VATS.

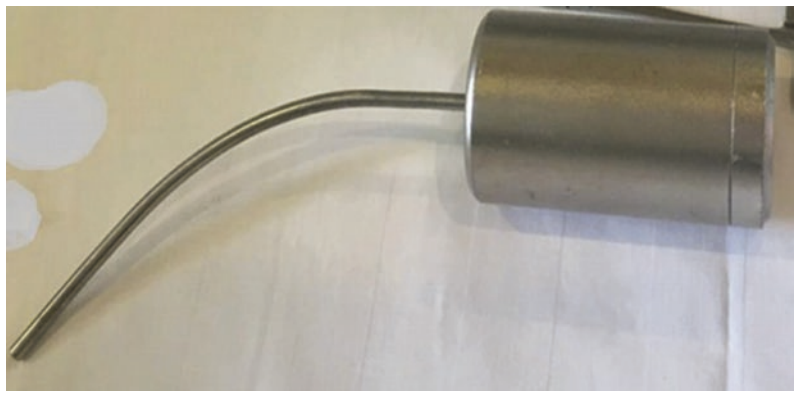

Fig. 5 Metal pot with long nozzle designed to deliver the water from outside the wound to deep inside the surgical field

Overall the SVATS approach for lobectomy could become a new tool in the armamentarium of the thoracic surgeon reducing pain and improving the post-operative quality of life meeting the necessary objective of our treatments.

Self-study

1. Which of the following statements is true?
   (a) SVATS has a higher rate of wound infection than VATS.
   (b) It is not possible to do lymph node dissection via SVATS.
   (c) Conventional VATS has higher rate of post-operative arrhythmia when compared to SVATS.
   (d) In current literature SVATS shows improved pain score than VATS to over a year.
2. Which of these would be a poor candidate for SVATS lobectomy based on inclusion and exclusion criteria?
   (a) T1N0 lesion in right upper lobe.
   (b) T2N0 in left upper lobe.
   (c) T1N0 leision in left lower lobe—known AF with cardiomegaly.
   (d) COPD patient with tumour <2 cm for segmentectomy.

Answers

1. Which of the following statements is true?
   (a) SVATS has a higher rate of wound infection than VATS–SVATS has a lower rate of wound infection.
   (b) It is not possible to do lymph node dissection via SVATS–SVATS can offer oncological sound pulmonary resection alongside lymph node resection.
   (c) Conventional VATS has higher rate of post-operative arrhythmia when compared to SVATS–SVATS has a higher rate of post-operative AF likely to compression and irritation of the heart particularly in left sided procedures.
   (d) In current literature SVATS shows improved pain score than VATS to over a year CORRECT.
2. Which of these would be a poor candidate for SVATS lobectomy based on inclusion and exclusion criteria?
   (a) T1N0 lesion in right upper lobe—T1 tumours are ideal for SVATS. The right upper lobe is also easy to access via SVATS.
   (b) T2N0 in left upper lobe—T2 tumours are in the inclusion criteria for SVATS. Although this is on the left hand side the upper lobe is easily accessible.
   (c) T1N0 leision in left lower lobe—known AF with cardiomegaly—CORRECT—there is high risk of dysarrthmia and cardiomegaly can obstruct your view and manipulation of the lung
   (d) COPD patient with tumour <2 cm for segmentectomy—SVATS is ideal for lobectomy in patients with tumour <7 cm or segmentectomy in leisions <2 cm.

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Minimally Invasive Pulmonary Resections Techniques—Nonanatomical Pulmonary Resections

Duilio Divisi, Mirko Barone, Luca Bertolaccini, and Roberto Crisci

Key Points

- Selected Patients with early peripheral NSCLC may benefit of limited resections.
- Tumor size, location and nodal involvement may contraindicate limited resections.
- Pre-invasive and early adenocarcinomas have almost 100% disease-free and overall survivals after limited resections.
- Anatomic segmentectomy and specimens' margin influences on patients' outcome.
- Long-term randomized trials are still needed.

Introduction

Several arguments over the extent of parenchymal resection have been waged in the treatment of Non-Small Cell Lung Cancer (NSCLC) aiming an en-bloc removal of cancer cells within lung parenchyma and locoregional lymph nodes. However, different factors such as diagnostics and surgical techniques improvements have strongly influenced current treatment of NSCLC with less invasive and calibrated resections arising questions about the end of the "pneumonectomy era". This aspect has described firstly in 1933 by Graham and Singer [1], as a result of additional attempt to minimize the extent of resection since 1960s. According to a pioneering landmark study by Ginsberg and Rubinstein [2], pulmonary anatomic resections (i.e. lobectomies) have been considered the standard of care for a proper surgical approach to lung cancer within a concurrent removal of lymphatic routes. However, the smaller pulmonary nodules have encountered more frequently in daily practice due to the advent of CT screening programs and the improvements in imaging arising different aspects about NSCLC surgical management. In fact, notwithstanding daily approach lies on a complete removal of primary lesion with an anatomical extension to lung parenchyma and locoregional lymph nodes according to vessel and bronchial features, sublobar resections such as segmentectomies or wedge resections have been proposed.

Non-anatomic Pulmonary Resections for Lung Cancer

Technical Aspects

Despite their similar classification, pulmonary wedge resections and segmentectomies'

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technical issues make them quite different especially concerning with hilum approach. Segmental resections require hilum dissection with division and suture of structures just like more extended anatomical procedures of pulmonary vessels and bronchi. Conversely, wedge resections are performed regardless broncovascular anatomy and pulmonary parenchyma is stapled without any identification of structures at distance of primary lesion (Fig. 1). Several factors must be weighed by considering non-anatomical resections for NSCLC. In sublobar resections, the parenchyma must be transected and divided for completion whereas, in lobectomy, the fissure must be divided to remove the entire lobe. This aspect arises limitations including tumor size, location and nodal involvement. Tumor size and local recurrence after sublobar resection have been extensively studied, having tumors larger than 20 mm a significantly higher local recurrence rate than smaller ones [3].

Bando et al. [4], studying 74 NSCLC sublobar-treated cases, showed patients with 20–30 mm tumors experienced a relapse risk almost 15-fold greater than less of 20 mm ones (33.0% vs. 1.9%, $p = 0.000$) with concomitant risks in overall survival (5y-OS $T < 20$ mm vs. $20 < T < 30$ mm: 92.9% vs. 63.0%). Another important factor influencing the applicability of non-anatomical resections is the tumor location, in relation to visceral pleura or hilum. According to a geometric fan-shaped segmental model apex-oriented towards the hilum, the distance between a neoplasm and the resection line should inevitably lie closer each other for hilar cancers; for these reasons a segmentectomy/wedge resection should be performed only for outer third lung tumors. Moreover, non-anatomical resection feasibility seems to be influenced by tumor location too. In particular, in a fascinating study enrolling 164 NSCLC patients intentionally treated with segmentectomies and comparing with 73 lobectomies [5], significant differences in outcome according to segmental location and side were reported. Local recurrences were 21.9% for right upper lobe, 10.5% for the left upper lobe, 4.2% for the apical segments of the lower lobes and 20.8% for basal segments of the lower themselves, supporting lobectomies for basal NSCLC cases. In this regard, some deeper and proximal lesions are not amenable for sublobar resections due to the absence of safe margins. In general,

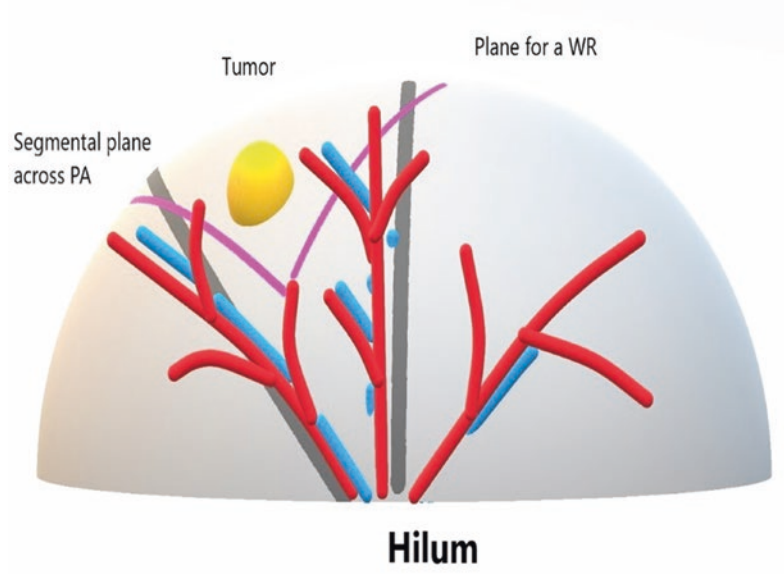

Fig. 1 Planes for pulmonary sublobar dissection. *WR* wedge resection

Table 1 Technical features for considering non-anatomical resections

Tumor size	CT < 20 mm
Location	Visceral pleura or hilum relationships Outer third lung tumors Upper lobes and apical segment lower lobe
Nodal involvement	Clinical cN0 (dimension and radiological criteria)[a]

[a]Dimensional criteria: lymph nodes >10 mm in short axis should be considered as pathological; however, adenocarcinoma nodal involvement frequently is not associated with increased dimension. Radiological criteria: finding upon radiotracers avidity in PET/CT scans. Also in this case low-avidity neoplasms should be considered

it should be considered only for peripheral T1a cancers (Table 1).

Oncological Aspects

Proposing a limited resection for the treatment of lung cancer faces with cornerstones, such as oncological radicality and long-term outcomes and historical established criteria as Halsted's ones. For these reasons, feasibility of non-anatomical pulmonary procedures for lung cancer still argues some questions even if in the current era, though they should be considered a consequence of the natural history towards minimization in thoracic surgery. But, does it deny or interfere with oncological radicality? Should a "compromise" strategy be overcome towards "intentional" strategies? Lung sparing resections have been always reserved for compromised and unfit patients who could not tolerate more extensive procedures. Churchill and Belsey [6] originally introduced segmental resections for the treatment of benign lung diseases, such as bronchiectasis, in 1939. Thirty-four years later, Jensik et al. [7] suggested a similar approach speculating about a presumed effectiveness and safety of surgical specimen margins for very small and peripheral primary lung cancers, determining questions and perplexity about the optimal management of very early-stage diseases. The first enthusiasm was immediately reduced by subsequent evidences. In fact, the Lung Cancer Study Group [2] carried out a randomized trial enrolling 247 stage I (T1N0) NSCLC patients and comparing feasibility and safety of non-anatomic resections with lobectomy. By clustering cases into two cohorts (n. 122 limited resections and n. 125 lobectomies), local recurrence was found in 17.21% (n. 21) of the first group and in 6.4% (n. 8) of the latter ($p = 0.008$). However, no significant differences were found according to non-local recurrence (13.93% vs. 12%, $p = 0.672$) and nor cancer-related death (24.59% vs. 16.8%, $p = 0.094$). Notwithstanding confusing results, Authors argued they failed to demonstrated the equivalence of non-anatomic resections to lobectomy and claimed anatomic excisions as the standard of care for NSCLC. This trial presented some selections bias, such as tumor dimension (up to 27,000 mm^3) and a significant number of wedge resections when compared with segmental ones (32.78 and 67.22%) and inducing to solidify lobectomy. So, though an increased interest about sublobar procedures grew closely to lobectomies, the previous were discouraged due to both a relapse incidence and patients' outcomes, as reported by Warren and Faber [8] in a cohort study on 173 early stage NSCLC. For these reasons, they were historically restricted only to impaired cardiopulmonary functions. However, recent investigations seem to contradict earlier results about anatomical sublobar resection. Campione et al. [9] found no significant difference in survival between lobectomy and anatomic segmentectomy in a series of 121 patients with stage IA disease. On the other hand, the aforementioned results seem to be historical and need a revision on the basis of the increased incidence with the introduction of high-resolution CT scans of early-stage patients (i.e. ground glass opacities), especially concerning the recent WHO classification of pulmonary adenocarcinoma. In this regard, the proposed role of non-anatomical resections of NSCLC is closely linked to some histological patterns, such as pre-invasive forms (minimally invasive adenocarcinoma, HAA, adenocarcinoma in situ) or pure lepidic or predominant lepidic of less

than 5 mm adenocarcinomas [10], characterized by almost 100% disease-free and overall survivals. Some reports about efficacy and oncological safety of wedge resections seem to confirm theoretical assumptions on augmented risk of recurrences and the only corroborating aspects are based on patients' outcome, as reported by Linden et al. [11] in a Society of Thoracic Surgery review. Enrolling 7,466 stage I-II NSCLC patients equally treated with non anatomic and anatomic resections (3,733 patients for each cohort), Authors reported overall 30-day mortality was 1.21% for wedge excisions versus 1.93% for anatomical one ($p=0.0118$) and also major morbidity rates showed similar trends (4.53% vs. 8.97%, $p<0.001$). These latter aspects were strongly highlighted by considering postoperative pneumonia (2.36% vs. 5.01%, $p<0.001$), the need for tracheostomy and ventilatory support (0.38% vs. 1.39%, $p<0.001$ and 0.51% vs. 0.91%, $p=0.039$) and septic risks (0.35% vs. 0.72%, $p=0.026$). Based on these evidences, they stated non anatomic resections carry a 37% and a 50% lower risk of mortality and morbidity, confirming some benefits for high risk patients. However, according to several retrospective institutional studies about pulmonary wedge resections, results are sometimes confusing. Kraev et al. [12], studying 289 NSCLC surgically-treated matched patients (215 lobectomies vs. 74 wedges), reported nonsignificant trend toward better survival in anatomic group versus wedge resection one (5.8 ± 0.3 vs. 4.1 ± 0.3, $p=0.112$) though, in the subgroup analysis of patients of up to cT1cN0, improved survival in lobectomy cohort was noticed ($p=0.029$). For these reasons, Authors claimed for a new randomized trials to confirm any superiority. Concerning with technical aspects affecting outcome, El-Sherif et al. [13], in a retrospective cohort study enrolling 81 NSCLC patients, speculated influence of margin distances as prognostic factor by clustering them into two cohorts (n. 41 with margin < 10 mm and n. 40 with margin > 10 mm). They report 14.6% (n. 6/41) of patients with margins less than 10 mm experienced local recurrences compared to 7.5% (n. 3/40) of those with borders greater than 10 mm ($p=0.04$), making them to support segmentectomy rather than wedge resections as these latter been usually associated with reduced free-distance margins. However, some distinctions must be considered. In fact, as far as the issue of sublobar-related margins safety, also occult malignancy in specimens' borders should be considered and, as reported by Sawataba et al. [14], positive cytological surgical margins could be assessed both in sublobar and anatomic resections, claiming further investigations. Maurizi et al. [15], in a retrospective study on 182 Stage I NSCLC patients wedge-treated, reported a regional recurrence of 26.4% ($n=48$), distant recurrence of 11% ($n=20$), a 5-year disease-free survival (DFS) of 51.7% and a 5y-overall survival (OS) of 70.4%. Moreover, Authors investigated influence of surgical margins by clustering population into three cohors (margins < 10 mm, 10 < margins < 20 mm, margins > 20 mm) finding any significant difference in regional recurrence, distant recurrence and overall survival ($p=0.9$, $p=0.3$ and $p=0.07$, respectively). They concluded that wedge resections are viable options for NSCLC surgical treatment in patients unfit for lobectomy and margins do not influence outcome when a R0 resection is achieved. In contrast, Mohiuddin et al. [16], in a retrospective study involving 479 patients, reported 1-, 2- and 3-year local recurrence rates, adjusted after censoring, of 5.7% (95% CI 3.1–8.1), 11.0% (95% CI 7.4–14.5) and 16.4% (95% CI 11.8–20.9), respectively. Analyzing any correlations between surgical margins and recurrences, they found a border greater than 15 mm significantly reduced any risk of relapses (margins greater than 15 mm vs. 10 mm: HR 0.41 vs. 0.55, $p=0.033$) and concluded that distance could be considered as safe for a surgical approach, being more wider distance not associated with statistical reduction of both local recurrence and cancer-related death (HR: 0.46 and 0.54, respectively). Although standard practice seems to refer sublobar resections as a compromised approach, some Authors reported intentional strategies even if in patients with normal lung functions (Table 2). Kodama et al. [17], in a 10-year retrospective cohort

Table 2 Indications for non-anatomic pulmonary resections

Necessity	Intentional
Compromised patients with limited cardiopulmonary reserve	Early stage NSCLC (up to cT1bN0 disease) Pure or partially-solid ground glass opacities Outer third up to cT1b neoplasms

Table 3 Sublobar resections for early stage NSCLC patients; outcomes' results

Author	Year	Patients	Sublobar/anatomic	LR[a] (%)	DR[b] (%)	5-DFI[c] (%)	5-OS[d] (%)	CRD[e] (%)
Ginsberg [2]	1995	247	122/125	17.21	24.59			24.59
Kraev [12]	2007	289	74/215				4.1 y	
Mohiuddin [16]	2014	479	479/0	16.40				
Kodama [17]	1997	140	63/77	13			93	
Koike [18]	2003	233	74/159	2.70	9.46		89.10	
Landrenau [19]	2014	624	312/312			16.70	54	

[a]LR: Local recurrence
[b]DR: Distant recurrence
[c]5-DFI: 5 years-disease free interval
[d]5-OS: 5 years-overall survival
[e]CRD: Cancer related death

study on 140 surgically treated T1N0M0 NSCLC patients (63 limited resections vs. 77 lobectomies), showed no different 5-years survival rates between groups (93% vs. 88%, $p=0.86$) as far as for frequency of local/regional recurrence (13.0% vs. 6.5%, $p=0.21$). Authors concluded that a non-anatomic approach with regional node dissections, should be considered for selected NSCLC patients. Similar results were published by Koike et al. [18], reporting outcomes of 74 up to cT1bN0 sublobar cases (n. 14 wedge resections and 60 segmentectomies) and comparing them with a lobectomy control group (n. 159). No differences nor in local neither distant recurrence were found (2 vs. 2, $p=0.42$; 3 vs. 7, $p=0.90$) as far as in cancer-specific deaths (5 vs. 8, $p=0.59$). Moreover, no significant differences in 3y- and 5y-OS between cohorts were found (94.0% vs. 97.0% and 89.1% vs. 90.1%, $p=0.91$). However, results seem to be slightly influenced by selections bias such as tumor size (1.5 ± 0.4 vs. 1.7 ± 0.4 cm, $p=0.001$). Landreneau et al. [19], in a propensity-matched score involving 312 segmentectomy patients and 312 lobectomy ones, reported lobectomy was associated with modestly increased freedom from recurrence (16.7% vs. 20.2%, $p=0.30$) and overall survival (54% vs. 60%, $p=0.258$), but without any statistical significance. In a meta-analysis, by Cao et al. [20], comparing sublobar resections versus lobectomy, effectiveness and safety of lung sparing approaches seem to be confirmed in NSCLC stage I. In particular, enrolling twelve studies and 2645 patients (1078 sublobars vs. 1567 lobectomies), no significant differences in overall survival (HR 0.91, 95% CI 0.64–1.29) or disease-free interval (HR 0.82, 95% CI 0.60–1.12) between the arms of the study. Moreover, segmentectomy cases' outcomes were similar to lobectomies (HR 1.04; 95% CI 0.66–1.63) (Table 3). These results could lay the foundation for starting new randomized controlled trials, which could revolutionize lung cancer surgery in this era of early detection.

Conclusions

Sublobar approaches to NSCLC still claim debate due to conflicting and sometimes confusing evidences. However, feasibility of non-anatomic resections should be considered by overcoming historical indications for impaired patients by enlarging them to high selected early stage NSCLC patients and reconsidering them towards intentional strategies rather than compromise ones. In this aspect, long-term randomized trials could afford definitive and exhaustive evidences, especially for what concerns anatomic segmentectomy and specimens' margin influences on patients' outcome.

Self-study

1. Factor influencing the applicability of non-anatomical pulmonary resections:
   a. Side
   b. Upper location
   c. Hilar distance
   d. Histology
2. Intentional non-anatomical pulmonary resections:
   a. Limited cardiopulmonary reserve
   b. Inner third up to cT1a tumors
   c. Early NSCLC
   d. None of them
3. Does nodal status influence applicability of non-anatomical resections?
   a. Yes
   b. No
   c. Only in cN2 disease
   d. Only in cN1 primary pulmonary adenocarcinomas
4. Which statement is a truth about Pre-invasive and early adenocarcinomas:
   a. have almost 100% disease-free and overall survivals after limited resections
   b. have almost 90% disease-free and overall survivals after limited resections
   c. have almost 80% disease-free and overall survivals after limited resections
   d. have almost 70% disease-free and overall survivals after limited resections
5. According to literature, significant differences in outcome (recurrence) according to segmental location and side were reported. A lobectomy is indicate for:
   a. upper lobes
   b. middle lobe
   c. lingula
   d. lower lobes

Answers

1. Factor influencing the applicability of non-anatomical pulmonary resections:
   a. Side
   b. Upper location
   c. Hilar distance
   d. Histology

   CORRECT: C. In case of central lesion, different studies show non feasibility due to absence of safe margins. Moreover, it is complicated to perform a non-anatomical resection due to risks of damaging hilar vessels or bronchi.
2. Intentional non-anatomical pulmonary resections:
   a. Limited cardiopulmonary reserve
   b. Inner third up to cT1a tumors
   c. Early NSCLC
   d. None of them

   CORRECT: C. Selected Patients with early NSCLC may benefit of limited resections because of minimal reduction of the pulmonary function with no risk of recurrence.
3. Does nodal status influence applicability of non-anatomical resections?
   a. Yes
   b. No
   c. Only in cN2 disease
   d. Only in cN1 primary pulmonary adenocarcinomas

   CORRECT: A. According to literature, nodal status, together with tumor size and its location, limits the applicability of non-anatomical resections.
4. Which statement is a truth about Pre-invasive and early adenocarcinomas:
   a. have almost 100% disease-free and overall survivals after limited resections

b. have almost 90% disease-free and overall survivals after limited resections
c. have almost 80% disease-free and overall survivals after limited resections
d. have almost 70% disease-free and overall survivals after limited resections

CORRECT: A. According to literature, pre-invasive forms (minimally invasive adenocarcinoma, HAA, adenocarcinoma in situ) or pure lepidic or predominant lepidic of less than 5 mm adenocarcinomas have almost 100% disease-free and overall survivals after limited resections.

5. According to literature, significant differences in outcome (recurrence) according to segmental location and side were reported. A lobectomy is indicate for:
   a. upper lobes
   b. middle lobe
   c. lingula
   d. lower lobes

   CORRECT: D. According to Nishio et Colleagues, lobectomies are suggested for basal NSCLC cases.

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Pulmonary Resections in the Extensive Pulmonary Pathology

Francesco Petrella and Lorenzo Spaggiari

Key Points

- Radical extended resection of lung cancer infiltrating closer structures—without lymph-nodal involvement—may offer encouraging overall survival results (5-year overall survival up to 56%).
- The chest wall is the most common neighboring structure involved by lung cancers and it is potentially amenable of radical resection in case of the absence of distant metastases or contralateral nodal involvement.
- Primary lung tumors infiltrating the diaphragm are very rare, accounting for less than 0.5% of the patients with locally advanced lung cancer.
- Although patients presenting with thoracic malignancies infiltrating the left atrium are rarely considered for surgical treatments, combined pulmonary and left atrium resections have been performed successfully both with and without the use of cardiopulmonary by-pass.
- Localized lung cancers infiltrating the thoracic aorta represent an even more rare entity than the already small category of other extended tumors and their treatment differs from other extended cancers because of the need for cardiopulmonary by-pass.

Introduction

Primary lung cancer is one of the most frequently diagnosed cancers and is the leading cause of cancer-related death worldwide [1]. Owing to the absence of clinical symptoms and effective screening programs, most lung cancers are diagnosed at an advanced stage [2].

The philosophy that radical surgical resection of all neoplastic tissue can be curative, even for extended lesions, has widely conditioned the therapeutic thinking of surgeons at the beginning of surgery and, to some degree, still remains alive in many surgeons at present [3]. On the other hand—however—the modern way to understand tumor biology and the prognosis of bronchial cancer, can lead to seriously question the value of such extended operations [3].

Anyway, complete tumor removal is the target of any surgical excision when treating lung tumors [4] and extended resections to structures contiguous to the lungs—as chest wall, vertebrae, diaphragm, superior vena cava and aorta—can be required to obtain macroscopic radical excision [5].

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These kind of extended resections—very often requiring pneumonectomy and contiguous structures resection—represent the most challenging surgical interventions in oncology, being both demolition and reconstruction technically demanding and usually performed by a multidisciplinary team (thoracic surgeon, cardiac surgeon, general surgeon and orthopedic).

This type of surgery, in fact, requires highly specialized centers, skilled surgeons, and skilled anesthesiologists, given the complexity of intraoperative and postoperative management [5]. Moreover these procedures are performed after induction chemotherapy and combined chemo-radiotherapy, that make tissue dissection more difficult and patients more fragile.

According to the 8th Edition of the TNM, lung cancers infiltrating the mediastinum, the diaphragm, the heart or great vessels, laringeal nerves, the trachea, the oesophagus and vertebral bodies are staged are T4 tumors and, in case of N0 or N1 involvement, they belong to stage IIIA whose overall survival after radical resection can be up to 41%; moreover, lung cancers infiltrating the chest wall, the pericardium or phrenic nerves are staged as T3 tumors and, in case of N0 or N1 involvement they belong to stage IIB or IIIA whose overall survival after radical resection can be up to 56% and 41% respectively [6] (Figs. 1 and 2).

However, postoperative morbidity and mortality remain high—almost doubled as compared with that of standard pneumonectomy [7] and so an accurate balance should always be performed before offering such procedures as the best treatment option.

Chest Wall

The chest wall is the most common neighboring structure byinvolved lung cancers [8] and its involvement is staged as T3 in the VIII Edition of the TNM, potentially amenable of radical resection in case of the absence of distant metastases or contralateral nodal involvement [6].

The most frequent oncologic indications for chest wall resection include primary or secondary chest wall neoplasms and contiguous involvement from breast or lung cancers [9, 10]. The basic principles for ideal management of complex post-resectional chest wall defects are rib cage reconstruction and soft tissue coverage.

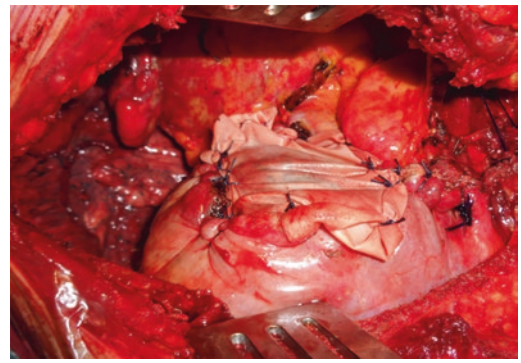

Fig. 2 Diaphragm resection and reconstruction by bovine pericardium

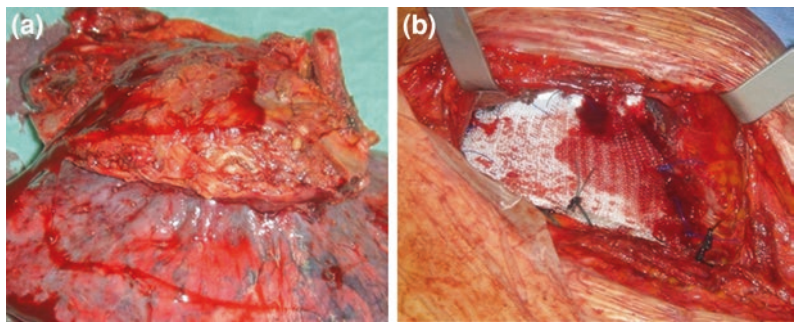

Fig. 1 En bloc chest wall resection with lung cancer (**a**) and reconstruction by composite rigid mesh (**b**)

Minor defects, or those located posteriorly under the scapula above the fourth rib can be treated by soft tissue alone, whereas larger anterior or lateral chest wall defects need prosthetic reconstruction. A wide range of synthetic prosthesis can be used to attain skeletal stability like methyl methacrylate sandwich, titanium bars, absorbable soft mesh, cadaveric allograft and three dimensional printed prostheses [11–13].

The optimal prosthesis should offer inertness, rigidity, malleability and radiolucency [14]. Although no material has been found to fulfil all the criteria, synthetic materials like Marlex mesh or Prolene are satisfactory for the reconstruction of medium-sized defects [9]. For extended demolitions, where structural integrity is paramount to avoid chest wall collapse, methyl methacrylate sandwich, Teflon, silicone, or acrylic materials have been utilized with good outcomes [15]. Although a plethora of synthetic materials can be used to stabilize the resected chest wall, there is no consensus on the most physiologic or effective structure. Wound complications such as infection, flap loss, dehiscence and hematoma are reported to occur in up to 20% of cases [16].

Superior Vena Cava

Although superior vena cava (SVC) infiltration by mediastinal and pulmonary neoplasms has long been considered a formal contraindication for surgical resection, experimental preclinical studies on large animals and case reports on humans—during 70s and 80s—demonstrated the technical feasibility of this advanced surgery [17].

In the case primary of lung cancers, muscle-sparing lateral thoracotomy is the preferred standard surgical approach, allowing even bronchoplastic or carinal resections while the hemiclamshell incision is the best choice in cases with right upper lobectomy. Median sternotomy or the hemiclamshell approach are indicated in the case of SVC invasion by mediastinal tumours [18].

The type and the extent of SVC resection depends on the degree of vascular infiltration. When venous involvement is less than 50% of its whole caliber, resection and direct repair is possible without excessively reducing the lumen of the SVC, by using mechanical stapling or running polypropylene suture on a vascular clamp.

When the defect is too large it is necessary to use of a pericardial patch to avoid excessive lumen reduction; moreover when the vessel is involved for more than 50% of its circumference, prosthetic replacement by cross-clamping technique is indicated. Only exceptionally cardiopulmonary bypass is required, when SVC infiltration involves the right side of the heart [19].

From the oncological point of view, the most conditioning prognostic factor is mediastinal nodal status: 5-year overall survival, in fact, is encouraging when there is no mediastinal involvement (N0 disease), disappointing in the case of pathologic N2 disease, and absent when contralateral mediastinal involvement is occasionally discovered during the hemiclamshell approach [18].

Although from the literature induction chemotherapy does not seem to offer any advantages, we suggest preoperative chemotherapy when SVC resection is planned: first, it can prevent metastatic spreading few months after resection, quite frequently seen when advanced lesions are operated on without any induction treatments; moreover the theoretical advantage of induction treatment—reducing cancer volume, increasing the chance of negative resection margins and sterilizing micrometastatic cancers—may facilitate resections and exclude patients with rapidly evolving disease from surgery [17–19].

Diaphragm

Primary lung tumours infiltrating the diaphragm are very rare, accounting for less than 0.5% of the patients with advanced locally lung cancer [20]. In our personal experience of 19 patients undergoing “en bloc” lung and diaphragm resection for primary lung tumours in a 12-year period, we reported a mortality rate of 5%, an overall morbidity rate of 63% and

a median survival and disease-free survival of 15 ± 9 months (range, 1–164 months) and 9 ± 7 months (range, 1–83 months), respectively. The 5-year Kaplan–Meier survival rate was 30 ± 11% while the 5-year disease-free interval was 34 ± 13%. Patients presenting only superficial involvement of the diaphragm had the best long-term prognosis (50 ± 18% superficial vs. 0% full-depth infiltration; log-rank test, P = 0.04) [20]. Our results—as previously reported by Yokoi et coll.—confirm that diaphragm resection is technically feasible and could be a valid therapeutic option with acceptable morbidity and mortality and long-term survival in highly selected patients suffering from NSCLC, when a complete resection is obtained [20, 21].

Left Atrium

Although patients presenting with thoracic malignancies infiltrating the left atrium are rarely considered for surgical treatments, combined pulmonary and left atrium resections have been performed successfully both with and without the use of cardiopulmonary by-pass [22–24].

Cardiopulmonary by-pass reduces the risk of clamp dislocation during left atrium manipulation—potentially resulting in lethal hemorrhage—and allows more extended resections, when needed, and adequate atrium reconstruction by patch; on the contrary it increases the risk of bleeding, acute lung injury and infections.

As with any patient undergoing cardiopulmonary by-pass, it is of paramount importance to identify significant synchronous valvular or coronary disease before the operation, potentially benefitting of surgical concomitant treatment.

From the technical point of view—in particular in case of right-sided tumors—it is important to take into consideration both the length of the interatrial groove as well as the distance of the cancer from the take-off of the contralateral pulmonary veins to avoid occluding veins during clamping and leaving adequate chamber volume [24]. To maximize the length of the atrial cuff, the epicardium between the right and left atrium—the interatrial groove—is dissected to lengthen the left atrial cuff according to the Sondergaard maneuver thus increasing the margin of resection and reducing the risk of clamping the right atrium [25].

The resection of left-sided tumors—when feasible—is easier and is accomplished through similar operative steps, except for the dissection of the interatrial groove and the extent of left atrium resection that is smaller, due to the position of the heart and its relation to the other mediastinal structures [24].

With regards to the oncologic aspects, the existing literature—although limited—demonstrates that in highly selected patients, extended pneumonectomy with partial left atrium resection ameliorate local control, with a definitive cure in some cases [24, 25].

Aorta

Localized lung cancers infiltrating the thoracic aorta represent an even more rare entity than the already small category of other extended tumors with infiltration of the vertebral bodies, the main carina or the apex of the chest [3]. Technical treatment of lesions invading the thoracic aorta differs from treatment of other extended cancers because of the need for cardiopulmonary by-pass, whose use may potentially contribute to scattering of tumor cells by aspiration of blood that is then returned to the circuit system. However both passive shunts as well as femoro-femoral extracorporeal membrane oxygenator (ECMO) can be used to prevent full anticoagulation of the patient during the resection and therefore the need for return of aspired blood into the system [3].

With regards to the oncologic aspects, the utility of induction treatments for advanced T3 and T4 tumors has been widely demonstrated, with the intent of downsizing larger tumors and eradicating undetected micrometastases; on the contrary, preoperatively diagnosed N2 cancers should directly be excluded from such an extended surgical procedure [3].

Klepetko et coll. demonstrated, in 1999, that combined resection of pulmonary cancers

infiltrating the aorta—with the use of cardiopulmonary bypass—can be performed with acceptable morbidity and mortality rates, showing effective local tumor control for N1 or single level N2 disease; however, long-term results were limited by systemic relapse [26].

Otha et coll. reported in 2005 a median survival time and 5-year survival of 31 months and 70%, respectively, for 10 patients with postoperative pathologic N0 disease and 10 months and 17%, respectively for 6 patients with pathologic N2 or N3 disease thus suggesting that in patients with N0 disease extended aortic resection is a valid procedure for selected patients [27].

Marulli et al., in 2007, in a multicenter study, showed that female gender and descending aorta invasion were independent positive prognostic factors and pneumonectomy—although feasible—was associated with a higher morbidity risk; moreover they reported that aortic endograft was a useful and safe technique allowing synchronous pulmonary and aortic resection without cardiopulmonary bypass or thoracic aorta cross-clamping, disclosing a lower, even if not statistically significant, morbidity rate, and a higher survival rate [28].

Vertebrae

Lung tumours infiltrating the vertebral bodies have long been considered to be unresectable but—thanks to innovative approaches for performing vertebral resection and spinal reconstruction—encouraging 5-year survival rates of 31–61% has been reported in several series [29–31].

Surgical excision alone is almost never an adequate approach for lung cancer with spinal involvement and must be combined with chemoradiotherapy.

En bloc partial and total vertebrectomy for lung cancer invading the spine remains a technically demanding procedure with significant post-operative morbidity that should be critically addressed before offering such aggressive procedure; however encouraging long-term survival suggests that en bloc resection could be a valid option in very selected patients with vertebral involvement of lung cancers [31].

Conclusions

Complete tumor removal is the target of any surgical excision when treating lung tumors and extended resections to structures contiguous to the lungs—as chest wall, vertebrae, diaphragm, superior vena cava and aorta—can be required to obtain macroscopic radical excision.

Multimodality approach—requiring chemotherapy, radiotherapy, combined chemoradiotherapy as well as new drugs together with surgical resection—is of paramount importance to offer the patients the best curative option.

Postoperative morbidity and mortality remain significantly higher than standard pulmonary resection and so accurate balance of risks and benefits should always be performed before planning extended pulmonary forresections lung cancers.

Self-study

1. Which statement is TRUE?
   (A) The chest wall is the most common neighboring structure involved by lung cancers.
   (B) Primary lung tumors infiltrating the diaphragm are very common (50%).
   (C) Thoracic aorta infiltration is a formal contraindication to lung resection.
   (D) Left atrium resections can be performed only under cardiopulmonary by pass.

   Answer: A
2. Which statement is FALSE?
   (A) Primary lung cancer is the leading cause of cancer-related death worldwide.
   (B) Most lung cancers are diagnosed at an advanced stage.
   (C) Lung cancers infiltrating the heart or great vessels are staged as T4 tumors.
   (D) Lung cancer infiltrating the chest wall are staged are T2 tumors.

   Answer: D

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Techniques for Pulmonary Metastasectomy

Bihter Sayan and Bedrettin Yıldızeli

Key Points

- In traditional electrocautery technique, complete resection is the key. Instead of VATS, thoracotomy is better in case of bleeding control.
- Laser is considered for patients with multifocal metastasis and it is a parenchyma saving method.
- In ultracision and ligasure techniques, thermal damage to the adjacent structures is minimal.
- Saline limits tissue heating to 1/3 of standart sealing methods.
- The thermoablative techniques do not require general anesthesia, cannot confirm tissue margins histologically and are valuable in patients with limited pulmonary function.

Introduction

The first pulmonary metastasectomy was published in 1883 by Perelman [1]. Since then, approach to pulmonary metastases has changed a lot. According to the European Society of Thoracic Surgeons (ESTS) metastasectomy working group, the evidence-based information available for guideline is insufficient; randomized controlled trials have not yet been completed. Currently, pulmonary metastasectomy is recommended for patients. Because, when systemic chemotherapy alone is used, long-term survival is rare. However, long-term survival was observed in patients undergoing surgical resection [2]. Yet, it still is a controversial issue due to lack of prospective data. Proof of oncological benefit requires a randomized controlled trial [3]. Five-year survival for all histologies is 36% [2]. Pulmonary metastasectomy is considered the only therapeutic option for curative purposes. Good results after pulmonary metastasectomy have been shown in many articles.

Some fundamental concepts about resection criteria according to Ripley's definition are:

- Primary disease should be controlled or seen as controllable,
- complete resection from the lung must be feasible,
- patient should be able to tolerate all the planned procedures,
- and the absence of a better treatment alternative are the resection criteria [2].

The predictors of favorable outcome are: disease free interval to be long (more than 3 years), a limited number of lung metastases and completeness of resection [2].

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In this chapter, we reviewed the pulmonary metastasectomy techniques as well as minimal invasive and open techniques.

Electrocautery

The technique was originally described by Perelman and published in 1883 [1]. It is designed to protect as much parenchyma as possible, because it should be kept in mind that re-metastasectomy may be required for the same patient at later course.

The resection with cautery should start from the nearest surface parenchyma. After demarcation of the surface parenchyma, the cautery line deepens to encircle the nodule. The nodule should be excised completely according to the main principles of metastasectomy (Fig. 1).

It is been advised to dissect when the lung is inflated. With inflation, removing more than enough functional lung tissue is avoided. On the other hand, inflation circumstance makes this technique not suitable for videothoracoscopy. Moreover, if the electrocautery fails to seal the vessels, it takes much more effort and requires experience to control bleeding by videothoracoscopy.

Laser

Laser assisted resection is a recent innovation defined especially for multiple pulmonary metastasis. In 1985, LoCicero established using laser in thoracic surgery [4, 5]. Their first research involved a carbon dioxide laser. Because it was a laser that only absorbed and cut, but not sealed, the technique was found

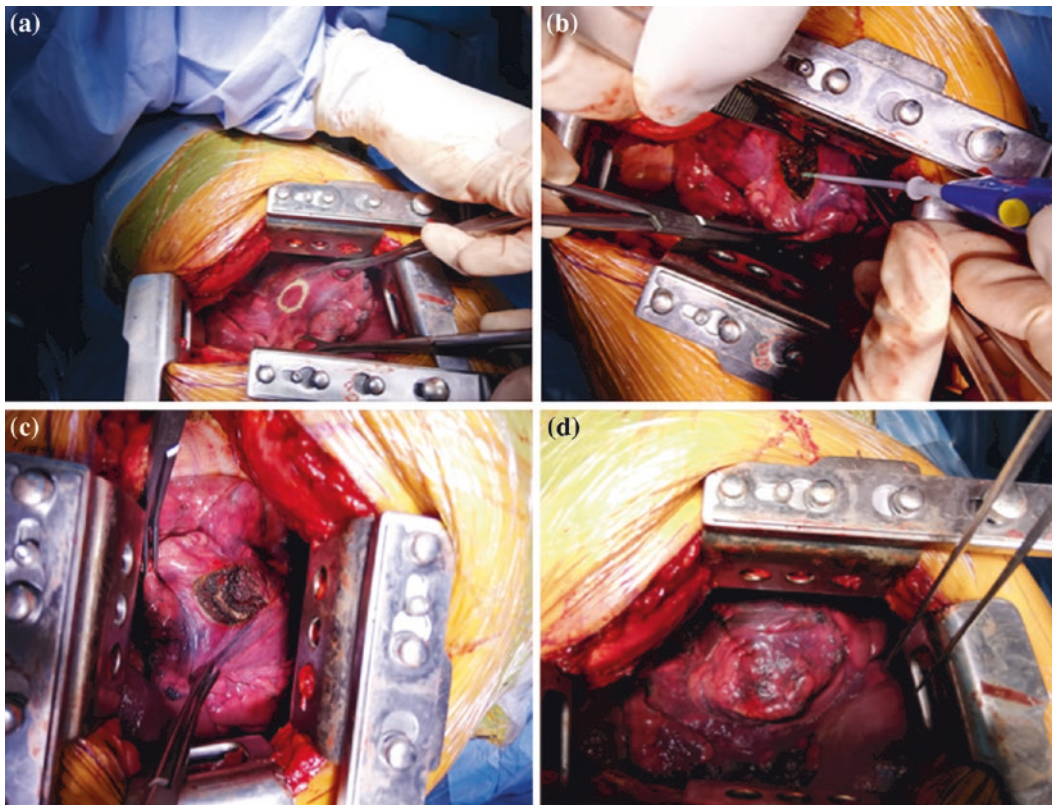

Fig. 1 **a** In an open surgery, the tumor is palpated and localized, **b** it is excised with electrocautery, **c** the cavity after the excision, **d** operation zone after capitonage

inadequate for lung surgery. Then American, Japanese and European researchers modified and upgraded the technique by using 1064 nm Nd:YAG laser. Although success came with superficial resections, the technique failed in central tumors [6, 7]. In the light of these first experiences, laser development started. Lung tissue's natural characteristics, high water content, low tissue density required different laser wavelengths to prevent bleeding and air leakage. Rolle et al. decided that 1318-nm laser is the only one to be considered suitable for lung resection surgeries [6]. Since 2007, improvements in nanotechnology allowed surgeons to use 1318-nm laser with high power output. So, operation duration became shorter and the postoperative photo thermal lung edema reduced [8].

Laser metastasectomy is usually performed by anterolateral thoracotomy. Bilateral lesions can be scheduled for two sessions with an interval of 3–4 weeks. All palpable nodules are found and removed from the collapsed lung. Working on a collapsed lung may result as resecting more peripheral lung tissue. But thanks to developed laser devices the surrounding healthy tissues' undesired resection is minimal. The nodules can be dissected at a distance of 2–3 mm from the tumor margin, reminding the one of the main principles of metastasectomy, to save the residual lung parenchyma. There is 5 mm necrosis rim. Kirschbaum et al. agrees with these findings by reporting YAG laser does less tissue damage than monopolar cautery [9]. So laser; unlike electrocautery, ligasure and ultrasonic devices, can be safely applied not only to the periphery of the lobe but also to the central lung without bleeding. Franzke et al. reported that in 17 patients (10%) in their series, a lobectomy could be avoided with laser metastasectomy [10]. With laser technique, the damage given to the adjacent lung parenchyma is minimal. Surgery can be performed to maximize the protection of the remaining healthy parenchyma with a limited excision in deeply located lesions. Moreover, lesions located near the major bronchus or vein can be removed with maximum margin with minimal damage to the surrounding tissue.

The disadvantages of the technique include the initial financial investment in the installation, the training of surgical team on safety issues, the requirement for a higher performance evacuation system and wearing protective goggles while performing surgery [8].

Metastases up to 8 cm can be resected by this method. It has been reported that up o 100 nodules in one lung can safely be removed [11]. Rolle and colleagues recommended the laser method if there were at least 20 metastases [12, 13]. Because 5-year survival was found 26% in their series. However, in Franke et al.'s series, the outcome is much more promising [10]. In their article, 99 laser and 79 non-laser patients were compared. The 5-year survival rate was 65.7% in laser and 73.6% in non-laser group. There was no significant difference in survival.

Moreover, the laser group was found to be at lower risk for local relapse [10]. In one-thousandth of a second, the temperature spread reaches 20–30 alveoli volumes. This causes the alveoli to shrink. The interstitial space, capillaries, small lymphatic and blood vessels close and thus the spread of the tumor is avoided [8]. Coagulation of the surrounding lung tissue by laser was thought to prevent possible local recurrence and explain the reduced local relapses. In Franzke's series, local recurrence was found much less in laser group (0.8%) compared to the rate of non-laser group (3.1%) [10].

It is known that the biology of primary cancer is a strong predictor of recurrence. Prognosis was found better in carcinomas than in sarcomas [7]. Additional therapies such as chemotherapy or radiotherapy are also predictive of survival. Branscheid et al. reported that the type of primary tumor, the disease-free interval, the number of metastasis and the potential degree of radical resection has positive impact on prognosis [7]. The number of metastasis (if greater than two) is an independent prognostic factor that increases the risk of recurrence [10]. There is no significant difference between wedge, segmentectomy and lobectomy [10]. In Franzke's series, different characteristics of the tumor were distributed equally to laser and nonlaser groups.

The series also showed no difference in terms of laser and non-laser postoperative complications.

Rolle et al. reported that laser should be considered when there is suspicion of remaining tumor [13]. Because it is thought that small satellite metastases can be obliterated by laser. It is generally not possible to confirm the negativity of the resection margins in the laser patients due to coagulation zone. Which means if the surgeon suspects recurrence after laser, it is not possible to histologically confirm that there are no tumor cells left. Therefore, only a clinical judgement can be made. In postoperative computerized tomography (CT) images, it is not possible to distinguish whether the residual tissue is harmless sequelae or relapse. However, in late postoperative period (such as 5–6 months), laser sequelae disappears and CT image improves. Clear evaluation of the margins can only be made in the late postoperative period.

It is widely accepted that survival indicator is complete resection. This ambiguity of the margins may lead to serious technical fault. On the contrary, Franzke's data showed that local recurrence in the laser group was statistically less, even if the negative margins were proven histologically in the nonlaser group [10]. Similarly, in Osei Agyemang group, although there were significantly more metastases excised in the laser group, there was no significant difference between the two groups in terms of overall survival [14].

The retention time of the chest tube in the laser group is slightly longer. Thus, the Franzke group recommends that the laser must be used in the presence of a large number of metastases that are localized centrally.

With the ability to preserve remaining lung parenchyma, laser method can also be used in patients who are not ideal candidates for surgery due to the limited lung function or multifocal metastasis. As a result laser, seems to minimize local recurrence, is also a good alternative resection technique in selected specific subgroups. Thus, indications may expand in the future.

Ligasure

Ligasure may be defined as electrothermal bipolar sealing system. It causes compression and obliteration of vessels with bipolar energy. With the fusion of collagen and elastin in the vessel walls, the tissue is reshaped and a definitive seal zone is formed without using staplers. The system automatically checks the thickness of the tissue and determines the amount of energy required for coagulation of the tissue, minimizing the energy in the surrounding tissue (1–1.5 mm) [8].

Although ligasure initially produced and improved for laparoscopic surgeries, it has been started to use in chest surgery. The device's head is smaller, so it is a natural advantage in videothoracoscopic surgeries. Kovacs and colleagues compared ligasure and endostapler for pulmonary wedge resection of solitary pulmonary nodules. They analyzed and compared the tissue margins. They reported that, the wall of the vessels is homogenous, structureless and intact. All of the resection margins were found to be complete [15]. Santini and colleagues confirmed their histologic results by reporting seal of vessels, with a mean depth of thermal injury limited to 1.1 mm [16]. The team showed dedicated efforts using Ligasure for pulmonary wedge resection, segmentectomies and bullectomies in both thoracotomy and videothoracoscopic surgery. They reported satisfactory results in both pre-clinical on pig lungs and clinical on human patients [16, 17]. Lacin T and colleagues proved successful sealing in even in pulmonary vessels less than 7 mm in size in an experimental setting [18]. Shigemura et al., holding the first published case report in the field [19] by using ligasure in a bullectomy, also reported good results in 12 human patient series [20].

According to Santini, this system has a better cost-effectivity [16] comparing ligasure with relatively novel technique: saline enhanced thermal sealing [21]. Kovacs compared ligasure with

endostaplers. He concluded that there is no more extra cost during surgeries, except the device's own cost [15].

The major disadvantage of ligasure is difficulty of excision of lesions located deeply in the lung parenchyma or near the hilum or large vessels [8].

By preserving lung tissue, having minimal thermal spread to adjacent tissues, providing good sealing zone, not increasing the surgery cost, facilitating the surgical procedure, ligasure can be named as a good alternative to staplers in non anatomical pulmonary resections.

Ultrasicion (Harmonic)

Ultracision is a technological advancement for cutting and coagulating tissue. Like ligasure, it first developed for abdominal and laparoscopic surgery.

Ultracision works by releasing energy from the device's tip. It creates a mechanical vibration. The mechanical energy transferred to the tissue. Thus, the tissue moves with high frequency generating heat. Rapid acceleration of tissue moving breaks the hydrogen bonds of the protein structure [22]. Denatured proteins results coagulation. Tissue is separated by creating steam bubbles while the temperature does not exceed 100 °C. The ultrasonic wave frequency is known 55.5 kHz [8, 23].

An additional advantage of this technique is that the heat dissipation sideways is low. Thus, lesions adjacent to vulnerable structures can be excised. Additionally, smoke generation is minimal [8, 24]. The speed of tissue separation can be controlled manually.

Aoki et al., had 20 limited pulmonary resection with harmonic scalpel, then sutured the cavitary with absorbable sutures. They reported that they did not have any further complications related to surgery [22].

Eichfeld and colleagues, reported excellent control of bleeding in coagulation zone [24]. They observed fibrinoid necrotic zones and obstructed blood vessels in the resection zone, histomorphologically. Their study was supported by Hayashi's experimental work [23]. Prolonged air leaks rate was very low according to Tajiri and colleagues [25].

According to Eichfeld and Hayashi, thermal damage to the surrounding tissue is minimal compared to the electrocautery and lasers [22–24]. It is suitable to use harmonic near greater blood vessels of the lung [23, 24].

In conclusion, with reduced lateral spreading of heat and reduced deep tissue damage, it is advised to use ultracision in lung parenchyma resection.

Thermal Sealing with Saline

It has been accepted in almost all surgical discipline that heat seals tissue. Recently, it has been shown that a continuous saline flow between device and tissue results coagulation. Saline couples electrical energy into tissue. Tissue converts electrical energy to thermal energy. To perform this technique, two new devices were introduced: a monopolar floating ball instrument and a bipolar sealing forceps [21]. These devices can be adapted to the Perelman's technique of non-anatomical lung resections.

One advantage of the technology is saline cooling the tissue. In traditional electrical sealing techniques, the tissue temperature exceeds 300 °C. In this technique saline limits heating to 100 °C or less [8]. Hence, surgeon avoids the needless tissue damage like char formation, cautery adherence, excessive damage to the surrounding lung parenchyma [8]. The smoke production is moderate [21].

This type of resection provides acceptable length of postoperative hospital stay and chest tube duration according to Yim's series [21].

Alternative Local Treatments for Pulmonary Metastasis Image-Guided Ablative Therapies

Technically unresectable tumors, patients who are not medically suitable for surgery due to comorbidity, those with short disease-free survival or those with extensive extrathoracic

disease are not suitable candidates for surgical metastasectomy [26]. It is appropriate to ablate pulmonary metastases in this group of patients by noninvasive or minimally invasive approaches. So, less invasive treatments are promised with this technique. But it is not known whether a complete eradication can be achieved. Negative margins cannot be confirmed histologically. The primary advantage of this technique is that it does not require general anesthesia.

The concept of oligometastatic disease was proposed by Hellmann and Weichselbaum [27]. Oligometastatic tumors are considered less likely to spread further. Patients with oligometastasis had better results than expected with ablative therapies. However, in only a few studies, the control group had oligometastasis and received systemic treatment (not directly to the metastasis), with no difference in survival [28].

Currently available types of thermo-ablative treatments are:

- Radiofrequency
- Microwave
- Cryoablation.

Radiofrequency Ablation (RFA)

The clinical experience with radiofrequency ablation was first introduced with liver. Then, the experience on lung tumors started to be reported. Nowadays, the most common thermal ablation technique used in lung is RFA. RFA has limited effect on pulmonary function. Because of that, patients who had recurrence after previous surgical intervention, might be a good candidate for ablation therapies avoiding morbidity of a second operation.

Ketchedjian et al. reported their experience in 33 tumors in 18 patients [29]. They initially used ablation by thoracotomy, then they converted their technique to CT-guided percutaneous ablation. They experienced one massive hemoptysis of a central nodule. Due to mortality in the follow-up period, they limited the use of RFA in tumors 5 cm or less. Many investigators agreed that, in metastatic lung disease, lesions larger than 3.5 cm were difficult to ablate.

Percutaneous thermal tissue ablation is performed with electrodes placed into the tissue under the guidance of radiological images. The electrode is inserted directly into the tumor. CT and magnetic resonance imaging (MRI) guidance are used for lesions located deep in the lung parenchyma.

Lung tumors are good targets for radiofrequency ablation. Because, the surrounding tissue makes a good isolation. Thus, energy can be concentrated in the tumor. As a result, adequate heating of the tumor is achieved with less energy compared to dense tissues such as liver. On the contrary, if there is a large vessel in the immediate neighborhood of the tumor, heat is removed. Thermal ablation of tumors near large blood vessels is affected by the cooling effect of blood flow, leading to incomplete ablation.

Gadalata performed percutaneous, CT-guided radiofrequency ablation in 63 primary and metastatic lung cancer patients [30]. They claimed complete tumor necrosis response in 92% of patients. But the follow-up period is only 9 months.

Although it is a low-risk and well tolerated technique, pneumothorax is the most common complication. Steinke et al. treated colorectal pulmonary metastases patients by radiofrequency ablation [31]. When the transcutaneous approach is applied, ten out of 23 patients developed pneumothorax (43%). Other complications include pain, hemorrhage, hemoptysis, prolonged air leak, acute respiratory distress syndrome (ARDS), reactive pleural effusion, damage to adjacent anatomic tissues, skin burns, infection and abscess.

The biggest limitation of RFA is to evaluation of the treatment response. Unlike surgery, in which the difference can be seen immediately after operation, it is often not possible to assess the treatment answer in the early term after RFA. Objective evaluation of treatment success is difficult. CT and PET can be used to evaluate treatment success at the end of treatment. Clinically, the lesion often appears bigger after ablation. Due to inflammation, edema, it

is difficult to determine whether it is residual or recurrent disease.

Ketchedjian et al. [29] described a selection criteria for RFA:

- Primary neoplasm should be controlled or controllable
- A thin cut helical CT scan
- Limited number of metastases (3 or fewer)
- All tumor nodules 5 cm or less
- Patient should be felt not to be a candidate for resection by thoracic surgeon
- Tumor nodules should be in the outer 2/3 of the lung (ie, should not abut mediastinum)
- All thoracic disease amenable to RFA.

The size of the ablated tumor was shown to be an independent factor for local tumor progression [32, 33]. The local tumor progression rate after lung RFA varies just as in literature, so in individual studies.

In conclusion, RFA preserves pulmonary function. It is associated with good local tumor control. But more prospective controlled trials are needed in the field. Until there is strong evidence on the contrary, resection should be standard of care.

Microwave Ablation (MWA)

It can be defined as thermocoagulation by electromagnetic methods. The device's frequency is equal to 900 MHz or higher. Radiofrequency is very similar to ablation; so, it is a heat-based tumor ablation method. Like RFA, microwave ablation can be performed with percutaneous (under sedation or general anesthesia) and open methods. Unlike radiofrequency ablation, microwave ablation gives thermocoagulation with electromagnetic wave. This causes a significant amount of oscillation of the water molecules in the tissue surrounding the active tip [34]. It is not necessary to ground the instrument because electromagnetic wave is used and electric energy is not used. Thus, a cautery plate (grounding pad) is not required. The risk of burns is eliminated.

One superiority of MWA compared to RFA is, MWA overcomes the heat-sink effect. Therefore, the treatment efficacy might increase. One group investigated the efficacy of MWA prospectively [35]. At 18 months they found the local control rate 73% for all of the histologies [35].

A study recently evaluated the safety and efficacy of lung MWA in 80 patients [36]. One year survival rate was 91.3% and two year survival rate was 75%. They added that there was no significant difference according to histopathologic type of primary tumor.

Cryoablation (Cryotherapy)

With an argon-based system, the tumor routinely receives 10 min freezing, 8 min active helium thaw, 10 min freezing cycles. The number of these cycles depends on the clinical case. A post-treatment CT scan is typically performed. The most popular use of the system is for the treatment of endobronchial lesions.

Cryotherapy's ablative effects were generated by tumoricidal pathways. These were defined as direct cytolysis due to ice crystal formation causing protein denaturation, intracellular dehydration and pH changes, ischemic necrosis via vascular injury, cellular edema and vessel disruption, activation of antitumor immune responses, and induction of cellular apoptosis [8, 37].

Wang and colleagues published their pulmonary data in a large cohort including all stages of lung cancer. Although the short term follow-up period cannot predict survival, the palliative benefits of cryoablation were reported. Another benefit of cryoablation over RFA and MWA, is the ability to preserve collagenous and other structural cellular architecture [37].

Cryoablation has been widely studied intraoperatively, with higher complication rates reported in hepatic malignancies when compared with RFA [38]. Although microvascular thrombosis occur after cryoablation procedures, bleeding requiring additional maneuvers reported in literature. Another

disadvantage of cryoablation is cost. Because argon gas is required for the procedure and more applicators were needed in comparison to RFA [39].

With advances in technology, new valid treatment options may be identified in the future, especially for the treatment of nonsurgical patient.

Sterotactic Radiosurgery (Cyberknife)

Patients with stage IV tumor disease were given systemic treatment without much survival expectation. After Hellman and Weichselbaum defined the term 'oligometastases' as an intermediate stage between locoregional and metastatic disease [40]. Some patients with oligometastatic disease was associated with favorable outcome.

Stereotactic body radiotherapy (SBRT) has a history of more than two decades. The effects of SBRT is well established in intracranial tumors and now in early-stage non-small cell lung cancer (NSCLC) too. SBRT is the treatment of choice in non surgical patients due to comorbidities or insufficient pulmonary function.

Recently, many published reports focus on SBRT's probable toxicity in ultra-central primary lung tumors. Colleagues from China published the largest single center data investigating for toxicity. Although it is difficult to identify toxicity attributable to SBRT, they reported two possible treatment-related deaths with cardiac causes [41]. SBRT with a moderate dose in 4–6 fractions is effective and tolerable for patients with advanced stage lung cancers [41]. However, caution should be taken especially in high risk patients.

Until recently, literature reports that the overall efficacy of SBRT is low compared to surgery. Plus, a complete radiologic response has been reported in only 9% of the patients with lung tumors and partial response in 65% of them [42].

The use of stereotactic radiosurgery in treating lung tumors is still relatively new. Most of the current literature on SBRT for oligometastatic disease is characterized by small patient cohorts with heterogeneous primary tumors.

According to Ripley, SBRT and RFA may be an alternative to surgical resection in pulmonary metastasectomy. SBRT irradiates the tumor with minimal damage to the surrounding tissue. Several studies have identified high local control with low toxicity. Small and solitary peripheral tumors are the best targets for SBRT [43, 44]. Rusthoven showed a phase I–II trial: applied SBRT to 1–3 lesions smaller than 7 cm [43].

According to a German multi-institutional data survival was significantly better for patients in good performance status, with small and single pulmonary metastases, long time interval between primary tumor diagnosis and SBRT treatment and favorable primary tumor histology [45]. Deck and colleagues reported that SBRT is well tolerated even in young age groups [46].

All in all, SBRT can be offered as an alternative treatment for medically inoperable patients with pulmonary metastases resulting in good local control and promising overall survival.

Open or Minimal Invasive Methods

Although a thoracotomy seems better by localizing the sites of disease properly by palpation, videothoracoscopy (VATS) is employed increasingly in metastasectomy. Eckardt and Licht agrees that vats are unsuitable because bimanual palpation is required in metastasectomy [47]. Small nodules can be missed. But Krüger and colleagues challenges that CT can see even the smallest nodules [48]. Another VATS concern is that lymphadenectomy can be performed inadequate in closed method but now many clinics gained experience in VATS. This is no longer a valid concern. There are many articles showing that there is no disadvantage in VATS [47–50]. One advantageous situation in VATS is recurrent surgery may be done easier in comparison to open methods. Postoperative faster recovery has also made VATS a good option.

Even after complete resection proven by histological examinations, 2 of the 4 patients with

local relapse in the stapler group were operated by VATS [10]. This can be used as a contradiction for videothoracoscopy. Moreover, computerized tomography (CT) scan may not show all of the lesions that can be discovered in thoracotomy [2].

Pastorino found more lesions during surgery in comparison to preoperative imaging [51]. Cerfolio reported that malignant nodules that did not appear on a 64-slice CT scan during thoracotomy [52]. Ellis found nodules that do not emerge in CT in the same way [53]. Reinhardt published high false negative results [54]. The Kayton [55] agreed emphasized that it may not be possible to detect all lesions by CT. According to ESTS inter-member survey, 65% surgeon considered the necessity of palpation in metastasectomy [56].

In conclusion, all of the treatment methods for pulmonary metastasectomy has advantages and disadvantages. Each method may be improved or some novel techniques may be added to the list in the future. Patients should be evaluated thoroughly. Multicentric prospective clinical trials may guide and lead to better survivals and quality of life.

Self-study

1. Which statement(s) is/are true regarding pulmonary metastasectomies?
   (a) Complete resection is the most important factor in predicting long-term survival.
   (b) A segmentectomy or a lobectomy may be chosen when lesion is centrally located.
   (c) A longer disease-free interval and limited number of lung metastases indicates a favorable outcome.
   (d) Thoracotomy's superiority to VATS is because of the advantage of bimanual palpation.
   (e) a, b, c, d.
2. Which statement(s) is/are true?
   (a) In laser, tumor-free margins cannot be confirmed histologically.
   (b) After radiofrequency ablation, due to necrosis, lesion always shrinks.
   (c) It is important to make a CT-scan immediately after radiofrequency ablation to measure the success of treatment.
   (d) In microwave ablation a grounding pad (cautery plate) is crucial because of the high risk of burns.
   (e) Radiofrequency and microwave ablations do not harm cellular architecture.

Answers

1. a, b, c, d are all true.
   (a) It is widely accepted that survival indicator is complete resection.
   (b) If the lesion is located centrally and cannot be excised completely without damaging adjacent vessels, anatomical resection may be an option. Because complete resection is the key.
   (c) The predictors of favorable outcome are: disease free interval to be long (more than 3 years), a limited number of lung metastases and completeness of resection.
   (d) Without bimanual palpation, small nodules can be missed in VATS.
2. Only option a is true. The other options are false.
   (a) If the surgeon suspects recurrence after laser, it is not possible to histologically confirm that there are no tumor cells left. Only a clinical judgement can be made.
   (b) The lesion often appears bigger after ablation due to inflammation and edema.
   (c) It is not possible to distinguish whether the residual tissue is harmless sequelae or relapse. However, in late postoperative period (such as 5–6 months), laser sequelae disappears and CT image improves. Clear evaluation of the margins can only be made in the late postoperative period.
   (d) Regarding MWA, it is not necessary to ground the instrument. Because electromagnetic wave is used instead of electric energy. The risk of burns is eliminated.
   (e) Benefit of cryoablation over RFA and MWA, is the ability to preserve collagenous and other structural cellular architecture. RFA and MWA's merit is necrosis.

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Approaches in Robot-Assisted Thoracic Surgery (RATS)

Ben Shanahan, Alexandru M. Cornea, and Karen C. Redmond

Key Points

1. The evolution of robotic surgical technology, and its use in minimally invasive thoracic surgery, is important to understand.
2. Staff selection and training, along with careful operating theatre setup is vital for the success of a RATS programme.
3. Care should be given to appropriate robotic instrument selection, with a wide range of thoracic robotic instruments available.
4. Port placement and patient positioning depends on the target lesion, with significantly different approaches for thoracic and mediastinal procedures.
5. The daVinci Xi platform offers significant advantages for the thoracic surgeon when compared to previous robotic surgical systems. The introduction of uniportal subxiphoid RATS represents the next step in development of minimal access thoracic surgery.

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Introduction

In the past all surgery on the chest was performed via an open approach, most typically via thoracotomy. Approximately 20 years ago Video Assisted Thorascopic Surgery (VATS) was pioneered for the first time for thoracic operations. VATS offered several distinct advantages over open approaches, with smaller incisions, no need to spread the ribs, reduced postoperative pain and shorter length of stay after surgery. Port incisions have become smaller over the years, with many surgeons now utilising a 5 mm camera and instrument ports for access. Incisions have also become fewer, and in more recent years the single-port VATS lobectomy has been developed, with a single port subxiphoid approach recently described, all in an effort to reduce postoperative pain and improve outcomes [1].

The focus of this chapter however is not on open or VATS surgery, as these have been extensively described elsewhere, but on robotic approaches to thoracic surgery. Simultaneous to the rise of VATS in thoracic surgery was the rise of robotic surgery in other specialties. Although the robotic platform initially focussed on cardiac surgery, more promising initial outcomes in urology, gynaecology and general surgery propelled the use of the robot in those specialties [2]. Thoracic surgery was not far behind, and the first robotic

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lobectomy was described by an Italian group in 2002 [3].

The history of robotic surgery stretches back as far as the 80s, when the first pre-programmable robot surgeon, the Programmable Universal Machine for Assembly 200 (PUMA) was employed to perform neurosurgical biopsies in 1985. Success with this initial application led to the use of the PUMA in urologic surgeries at Imperial College London. Following on from the success of the PUMA, other platforms such as the Surgeon Assistant Robot for Prostatectomy (SARP) and Prostate Robot (PROBOT) were used in prostatectomy. All of these systems had to be pre-programmed and operated based on fixed anatomical landmarks in the patient. Thus they were poorly suited to dynamic surgical targets, such as those found in thoracic surgery [2].

In the 1990s robotic surgical technology progressed with the development of several 'master-slave' surgical systems. These consisted of patient manipulators controlled by surgeons at a remote workstation. The Automated Endoscopic System for Optimal Positioning (AESOP) was approved by the FDA in 1994. It was an endoscopic camera manipulator controlled by the surgeons' voice commands, and this obviated the need for a scrubbed assistant to control the camera.

The natural progression from the AESOP was the addition of surgical instruments capable of reproducing a surgeon's arm movements to the system. This was achieved with the Zeus platform, first used for a fallopian tube anastomosis in Ohio in July 1998. Interestingly the Zeus also performed the first ever transatlantic tele-surgery, with a laparoscopic cholecystectomy performed on a patient in Strasbourg by a surgeon in New York. In 2003 Computer Motion Inc. developers of the AESOP and ZEUS, merged with Intuitive Surgical Inc., and the ZEUS was discontinued [2].

The daVinci surgical system, developed by Intuitive Surgical Inc, is the most widely used robotic surgical platform currently on the market, with over 4,400 daVinci platforms in use worldwide [4]. The system prototype, 'Mona', was used in Brussels in 1998 to perform a robot-assisted cholecystectomy. It went on to be used in cardiac revascularisation procedures at the University of Leipzig in 1998. Following FDA approval, and the success of the first robotic radical prostatectomy in the USA in 2000, the daVinci gained popularity in pelvic surgery (urology, gynaecology and general surgery) in the early part of the 21st century [2].

The first thoracic surgical experiences with the daVinci system were reported in 2002 by Melfi et al. Initial applications included lobectomy, tumour mass excision and bulla stitching for spontaneous pneumothorax [3]. Robot Assisted Thoracicsurgery Surgery (RATS) has come a long way since those early days. There is now high quality evidence from systematic reviews that RATS is a feasible and safe approach for lobectomy in selected patients, with equivalent short term oncologic efficacy to VATS [5]. Indeed a recent meta-analysis by the author comparing RATS, VATS and open lobectomy found RATS to be superior to VATS with respect to 30-day mortality [6]. A recent meta-analysis addressing approaches for Thymectomy found RATS to be a valid alternative to open surgery, with advantages including reduced blood loss, fewer post-operative complications complications, a shorter hospital stay, and lower positive margin rate [7].

The high initial start-up costs associated with RATS, and in particular with the daVinci platform, are seen as its principal drawback. Further high-quality economic analysis is needed to properly address this issue, and evaluate the cost-effectiveness of RATS lobectomy. The author has a project ongoing to address this question, and hope to publish results in the coming months.

Although Intuitive Surgical Inc. has dominated the robotic surgery market thus far in the 21st century, competing systems are currently under development by companies such as Medtronic (USA), Cambridge Medical Robotics (UK) and TransEnterix (USA), among others. Having said that the daVinci Xi system is the only one currently in widespread use for

thoracic surgery, and as such it shall be the focus of the remainder of this chapter.

Recent concerns have been published by the Food and Drug Administration (FDA) in the US, highlighting the mixed results of some robotic surgery trials for urologic cancer. The FDA warns that the safety and efficacy for of robotic surgery in the treatment of cancer has not been fully established, and more investigation is needed [8].

Robotic Programme Development

Key to the establishment of a successful RATS programme is selecting and training the right staff. Intuitive offer training courses for nursing, technical and surgical staff. Indeed there is a minimum level of training that the company deems mandatory before an institution can start a RATS programme, which comprises eLearning, console training and case observership. In addition to this, proctoring is offered to a team as their programme is getting off the ground. This distinguishes the daVinci platform from other surgical technologies, with which there is more commonly a 'learn as you work' approach. It also helps to maintain practice and safety standards.

Staff Considerations

Key theatre staff members include:

1. Operating surgeon
2. Primary assistant
3. Scrub nurse
4. Circulating nurse
5. Anaesthetist
6. Anaesthetic nurse
7. CSSD staff.

The above list is by no means exhaustive, and certain staff members may or may not be needed depending on local policies and procedures. For example certain surgeons prefer their primary assistant (who is scrubbed at all times) to be of a level of proficiency where they could begin to open the chest themselves in an emergency while the senior operating surgeon scrubs up. However, at our institution the surgical assistant is a junior resident or more usually an Advanced Surgical Practitioner. In an emergency, a quick surgical scrub for the operating surgeon does not cause any significant delay, occurring whilst the robot is being un-docked and the thoracotomy tray opened.

Theatre Layout

The equipment and staff setup in theatre is outlined in Fig. 1.

The above diagrams outlines the setup at our institution-there may obviously be local variation depending on space constrictions in different units. The author prefers to have the console arranged so that he/she can easily turn to the right to view the theatre set-up and vision cart screen at all times. It is important to consider the final theatre layout prior to bringing the patient into the room, as it can be difficult to manoeuvre the daVinci patient cart once the operating table, scrub trays, vision cart etc. are all in place.

It is usual practice that the robotic equipment is kept in a dedicated theatre supervised by a dedicated robot coordinator, and that all instrument sets, consumables and other equipment that may be necessary during a case are kept in designated places in that theatre. This allows staff to quickly locate and access the necessary equipment; important for the efficient running of a theatre, and potentially life-saving in an emergency. The theatre setup may need to consider the need for perfusion support during an emergency.

Robot Targeting

Robotic targeting is the procedure in which the robot and arms are moved into position at the beginning of a procedure. Depending on the model of robot used, this can be a time-consuming process, especially as one is becoming familiar

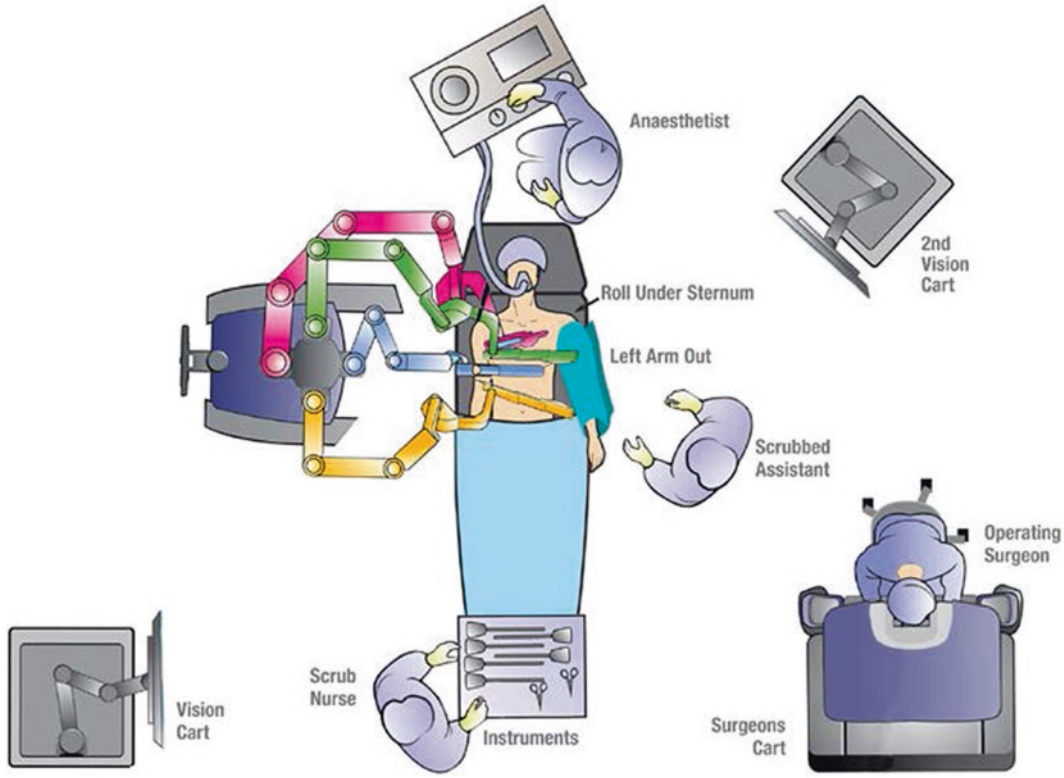

Fig. 1 General theatre equipment and staff setup for robot assisted thoracic surgery

with the robotic equipment. The latest daVinci model, the 'Xi', features a laser targeting system, which greatly contributes to reduced setup time, usually less than 15 min [9].

Robotic Instruments

Intuitive Surgical provides a wide range of instruments for use with the daVinci Xi system. The following are some of the more commonly used instruments used for robot assisted thoracic surgery, however this list is by no means exhaustive:

Endo Wrist Stapler

Small graptor (grasping retractor)

Double fenestrated grasper

Cadiere forceps

Monopolar curved scissors

Permanent cautery hook

Permanent cautery spatula

Curved bipolar dissector

Maryland bipolar forceps

Fenestrated bipolar forceps

Harmonic shears

Vessel sealer

Suction irrigator

Patient Positioning and Port Placement

When considering port placement for robot assisted thoracic surgery, there are two overall approaches. The first approach is the standard approach for lobectomy, lung volume reduction surgery, and other procedures performed in the hemithorax. The second approach is for thoracic surgery performed in the mediastinum, the most common of which is thymectomy.

Patient Positioning and Port Placement for Approach to the Hemithorax

Approach to Right Hemi-thorax

Patient Position

- The patient is positioned left lateral decubitus, with a 5–10 degree break in the table. The break should be at the base of the thorax.
- The table should be as low as possible for the docking procedure. Theatre light fittings need to be positioned in such a way as to avoid clashing with the patient cart.
- The patient cart approaches from the back of the patient (right side of table), as can be seen below (Fig. 2).

Port Placement

1. The camera port (3) is placed first, between the mid axillary line (MAL) and anterior axillary line (AAL). For upper lobe procedures the 7th or 8th intercostal space (ICS) may be used (as in the diagram), however for middle and lower lobe procedures we recommend the 8th ICS. It is important to review imaging pre-operatively to ensure the camera port is placed above the diaphragm.
2. The endoscopic camera is inserted and hemithorax evaluated. CO_2 is insufflated to a pressure of 6–8 mmHg. Haemodynamic instability may occur at this point, and should be monitored for.
3. All other ports are placed under direct vision. Ports (1) and (2) are placed posterior to port (3), ideally in the same intercostal space, with each port being placed 6–10 cm apart (Xi). A minimum space of 4 cm must be maintained between port (1) and the spine. The more posterior the port (posterior ports are usually 8 mm) the higher the risk of an intercostal bleed, as the intercostal space (ICS) is narrower.
4. Port (4) is then placed 6–10 cm anterior to port (3) in the same ICS.
5. The author uses Serratus muscle or Erector Spinae muscle blocks as part of an enhanced recovery after surgery (ERAS) programme to facilitate good pain relief and early discharge.
6. The author uses a 12 mm port for 2 and 4 to facilitate stapling in both directions and swab exchange, with an 8 mm port in

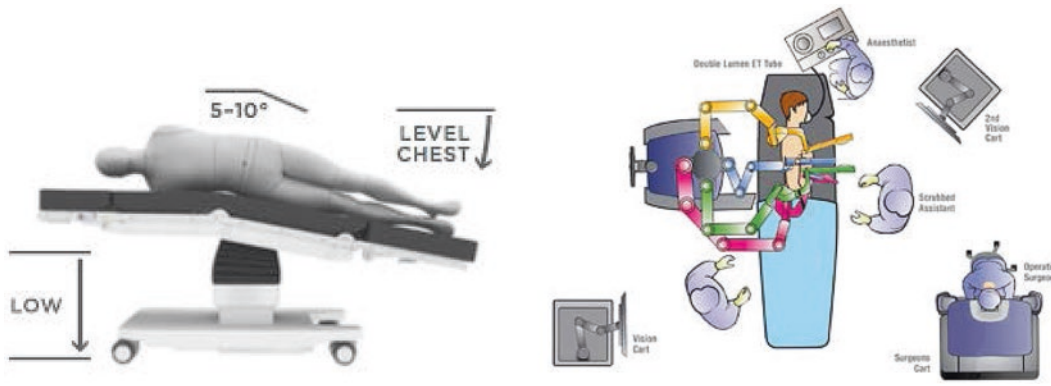

Fig. 2 Patient position and theatre setup for robotic approach to the right hemi-thorax

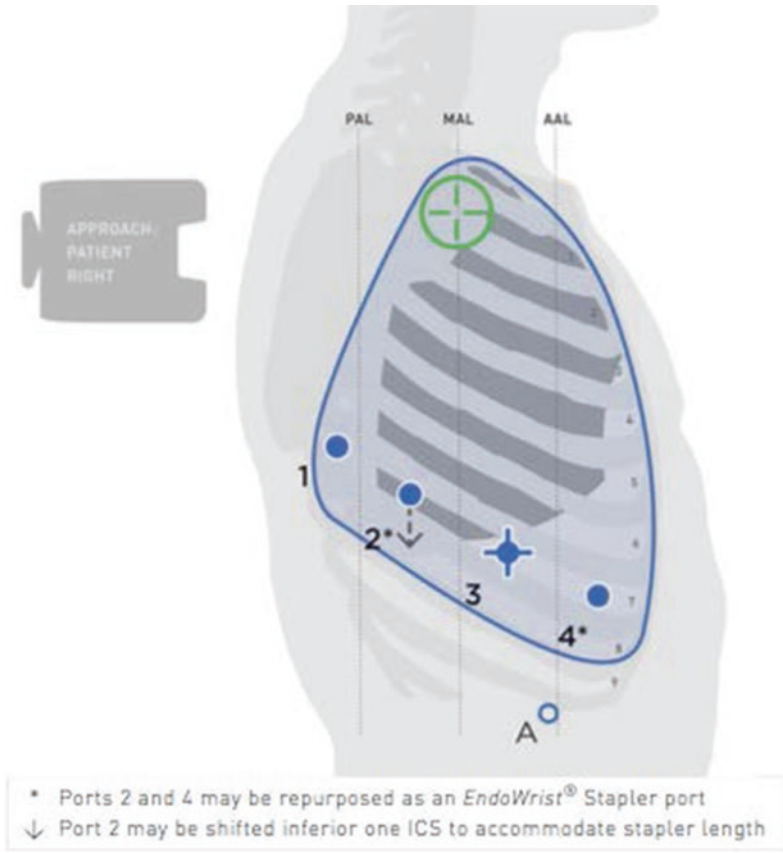

Fig. 3 Port placement for robotic approach to the right hemi-thorax

locations 1 and 3. No other ports are used. However, an optional 12 mm assistant port may be placed as inferiorly as possible, at the junction of the diaphragm and chest wall towards the subxiphoid location for additional non-robotic thoracoscopic access and specimen removal. This port should be approximately triangulated between ports (3) and (4). This is not routinely done, port 4 is extended to remove the final specimen (Fig. 3).

Approach to the Left Hemi-thorax

Patient Position

- Positioning is similar to the right sided approach, except the patient is positioned right lateral decubitus. The robot and arms again come in from the right (Fig. 4).

Port Placement

See Fig. 5.

Patient Positioning and Port Placement for Approach to the Mediastinum

Patient Positioning

- The patient is positioned supine with the patient's flank at the break in the table.
- A roll or wedge is placed under the mid thorax in order to drop the shoulder, lift the thorax, and spread the intercostal spaces.

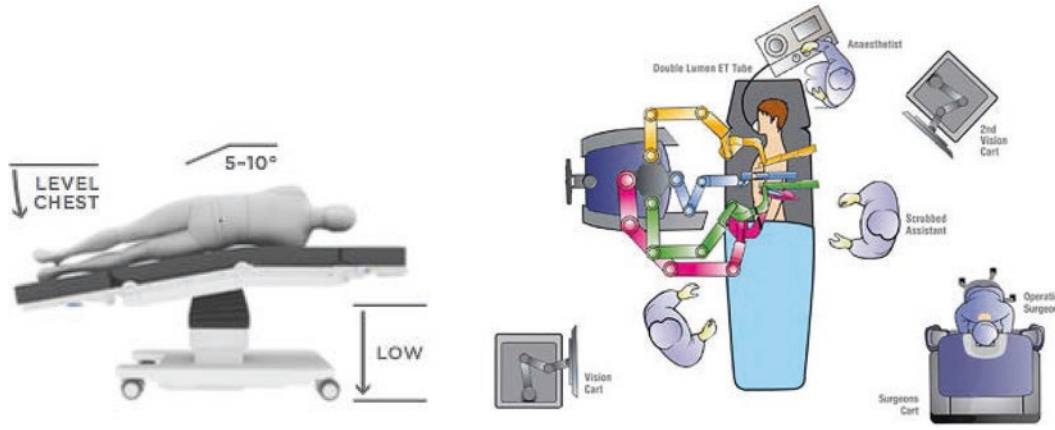

Fig. 4 Patient position and theatre setup for robotic approach to the let hemi-thorax

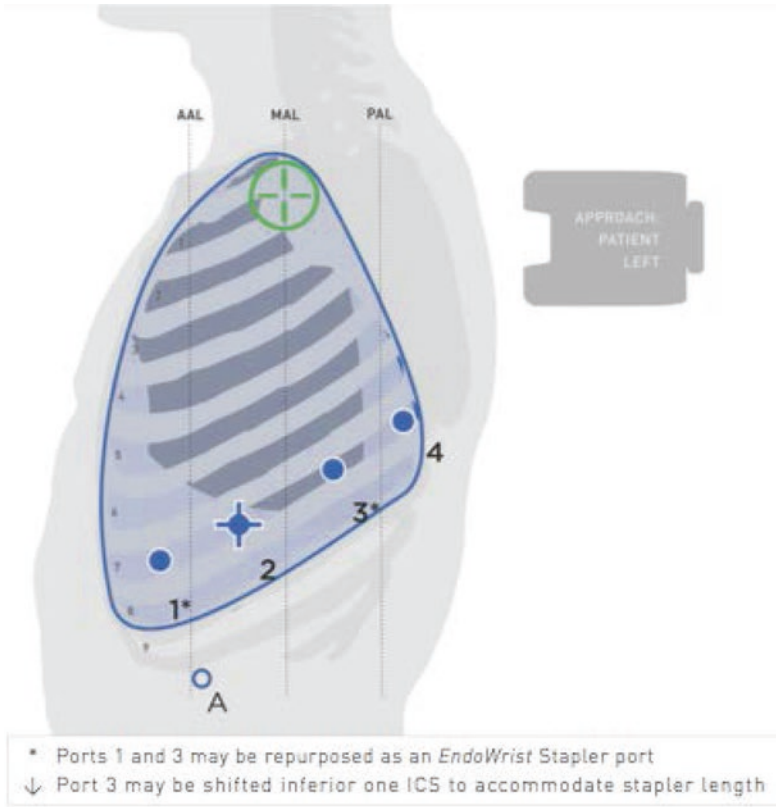

Fig. 5 Port placement for robotic approach to the left hemi-thorax

- The patient should be positioned as close as possible to the edge of the table on the side being operated on. The arm on this side is flexed slightly and allowed to hang below the table at the level of the table rail (as outlined in Figs. 6 and 7). This arm should be secured with a sheet wrapped around the arm and then gathered under the patient. The contralateral arm is positioned at the level of the patient also using a sheet.

- The table is rotated 15 degrees toward the operative side, and is set as low as possible, with slight reverse trendelenburg.
- The patient cart approaches from the contralateral side to that being operated on, as seen in the image above (right side of table approach to perform a thymectomy from the left hemithorax). The robotic arms then reach over the patient, and ports are placed on the operative side (Fig. 6).

Port Placement for a Left Sided Approach to the Mediastinum

1. Place the camera port first. Ascertain the midpoint of the sternum, halfway between the manubrium and the xiphoid process. Place the camera port in the interspace 1–2 ribs below the midpoint of the sternum, slightly medial to the anterior axillary line, at the lateral aspect of the breast. In a woman the breast is taped up superiorly and the access point is just below the mid-point of the submammary fold.
2. The endoscopic camera is inserted carefully to avoid the heart, and all other ports are placed under direct vision following CO_2 insufflation.
3. The remaining 2 ports (one 8 mm (8 cm medially) and one 12 mm (8 cm laterally) for swab exchange) are inserted maintaining the curvature of the line of the breast (Figs. 7 and 8).

The Future

The arrival of the daVinci Xi platform has been a huge leap forward for RATS. The Xi system is the first platform designed specifically with the needs of thoracic surgery in mind, and there are

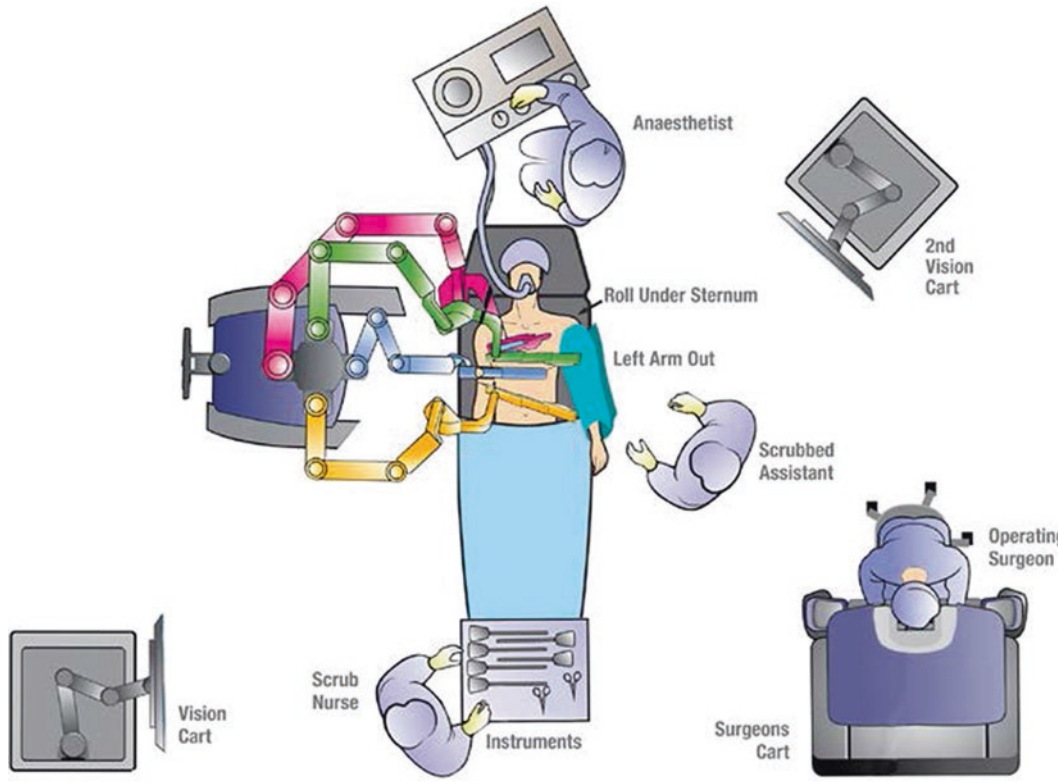

Fig. 6 Patient position and theatre setup for robotic approach to the mediastinum

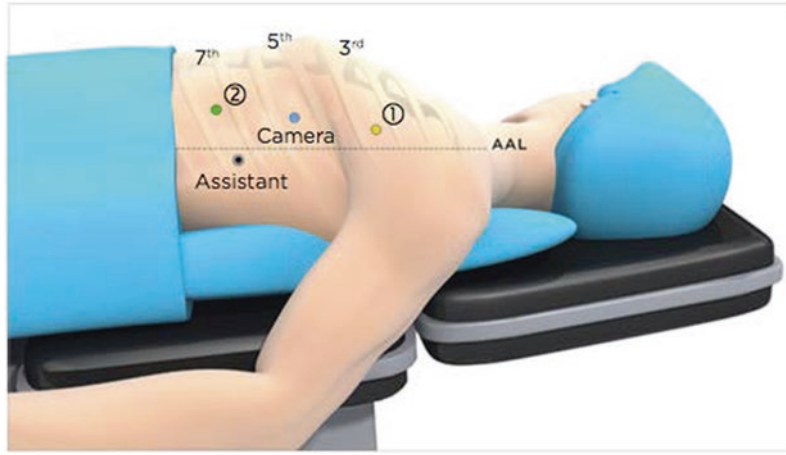

Fig. 7 Port placement for left sided approach to the mediastinum

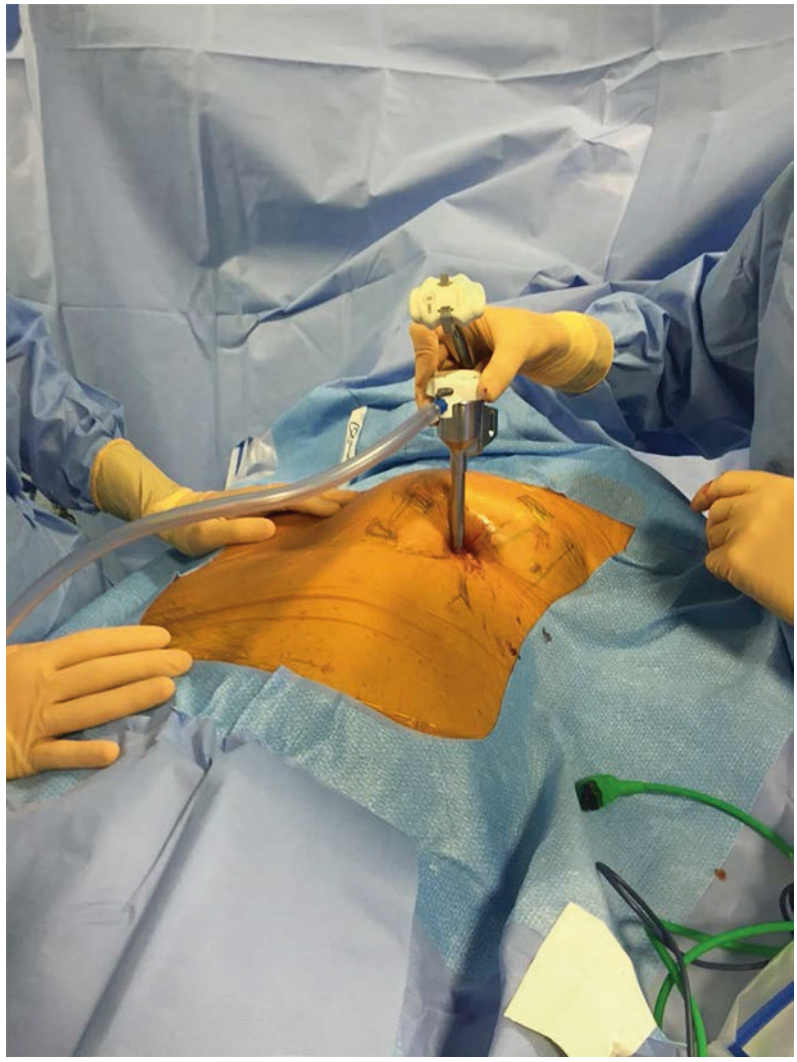

Fig. 8 Image demonstrating port placement for left sided approach to the mediastinum

several significant advantages when compared to previous daVinci models:

1. Automatic targeting (discussed earlier in this chapter), streamlines the setup for thoracic operations, improving operative efficiency.
2. The Xi allows for port-hopping with the camera-that is to say that the endoscopic camera can be used on any of the robotic arms/ports. This is very useful when trying to 'see around corners', or in those situations where the operative view just isn't quite right.
3. The Xi is the first platform to facilitate robotic stapling—previously the primary assistant would operate a traditional VATS stapler via the assistant port. Robotic stapling enhances the control that the operating surgeon has over the procedure, improving both efficiency and safety. Intuitive "Endo Wrist" technology gives the robotic stapler greater range of articulation than a traditional VATS stapler, with 108 degree vertical and 54 degree horizontal articulation, allowing the surgeon to achieve those awkward stapling angles so often encountered in thoracic surgery. "Smart Clamp" feedback enhances control even further, and tremor reduction technology limits tissue damage caused by minute, unintentional hand movements.
4. The Xi platform is the first to offer "Firefly" intraoperative perfusion assessment technology. This involves the injection of indocyanine green (ICG) tracer into the blood via a central line, with subsequent detection via a near-infrared camera mounted on the daVinci endoscope. ICG is confined to the vascular system, has a half-life of 3–4 minutes, and is eliminated to the liver [10]. The authors have successfully employed this technology in Lung Volume Reduction Surgery (LVRS), using real-time intra-operative perfusion assessment to target resection, and have published their technique [11].

There has been a gradual trend in minimally-invasive thoracic surgery toward uni-portal surgery over the last several years. An example of this is the sub-xiphoid uni-portal approach to lobectomy described by Ismail et al. [1]. This trend is driven by the need to reduce postoperative pain, shorten length of stay and hasten return to work/daily activities for our patients, all while maintaining excellent oncologic outcomes. The manufacturers of robotic surgical systems are also following this trend, with purpose-built uni-portal robotic platforms such as the daVinci SP under development. The authors feel that this uni-portal robotic technology will feature prominently in the future landscape of thoracic minimally invasive surgery.

Self-study

1. Which of these statements is UNTRUE:
   - The daVinci robotic system was originally intended for use in cardiac surgery.
   - Robotic surgery offers the only minimally invasive approach for thoracic procedures CORRECT.
   - The surgical robot and associated equipment should be kept in a dedicated operating theatre.
   - Staff considerations are key to the development of a successful robotic programme.
   - Laser targeting reduces the set-up time for the daVinci Xi robot.
2. Regarding the approach to the right hemi-thorax, which of the following statements is UNTRUE:
   - The patient is positioned right lateral decubitus CORRECT.
   - The table should be as low as possible.
   - There should be a 5–10 degree break in the table at the base of the hemi-thorax.
   - The robot patient cart approaches from the patient's back.
   - CO_2 is insufflated to a pressure of 6–8 mmHg.
3. Which of the following is NOT a daVinci instrument used in robotic thoracic surgery:
   - Cadiere foreceps.
   - Vessel sealer.
   - Permanent cautery hook.
   - DeBakey foreceps CORRECT.
   - Harmonic shears.

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Embryology and Anatomy of the Pleura

Claudiu E. Nistor, Adrian Ciuche, and Ecaterina Bontaș

Key Points

- The pleural cavity is created between the 4–7 weeks of embryologic development
- Intraembryonic coelom or coelomic cavity develops as a space in lateral plate mesoderm which develops into the 3 main body cavities: pleural, pericardial and peritoneal
- Parietal and visceral pleura have separated embryological development. Both visceral and parietal pleurae derive from the lateral plate mesoderm which splits into two layers the somatopleuric mesoderm forming parietal pleura and the splanchnopleuric mesoderm of visceral pleura
- Parietal pleura is distinguished from visceral pleura by the presence of stomas and sensory innervation.

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Embryology

The first stages of human life are divided into the ***embryonic*** and ***fetal*** periods. ***Embryonic stage*** defines first 9 weeks of life, followed by ***fetal stage*** until birth. The **embryonic** period extends from fertilization to week 9 being characterized by gastrulation, neurulation and folding of the human embryo. The ***fetal*** period lasts from the end of week 9 to birth. Pleural cavity is created between the 4–7 weeks of embryologic development [1]. Parietal and visceral pleura have separated embryological development.

1–2 Weeks

During the first 14 days, the human embryo is a bilaminar disk that comprises (1) the endoderm; and (2) the ectoderm, where the endoderm is covering the yolk sac (Fig. 1) [2].

Week 3.

At the ***onset of 3***rd ***week (stage 10)***, it happens ***gastrulation*** by which the bilaminar human embryo turns into three-layered (trilaminar) disk by development of the third layer named the mesoderm (Fig. 1) [2, 3].

At ***the end of third week of gestation***, before body folding, the mesoderm of human embryo becomes condensed and develop two longitudinal forms named the ***paraxial mesoderm***. Initially, the mesoderm differentiates into

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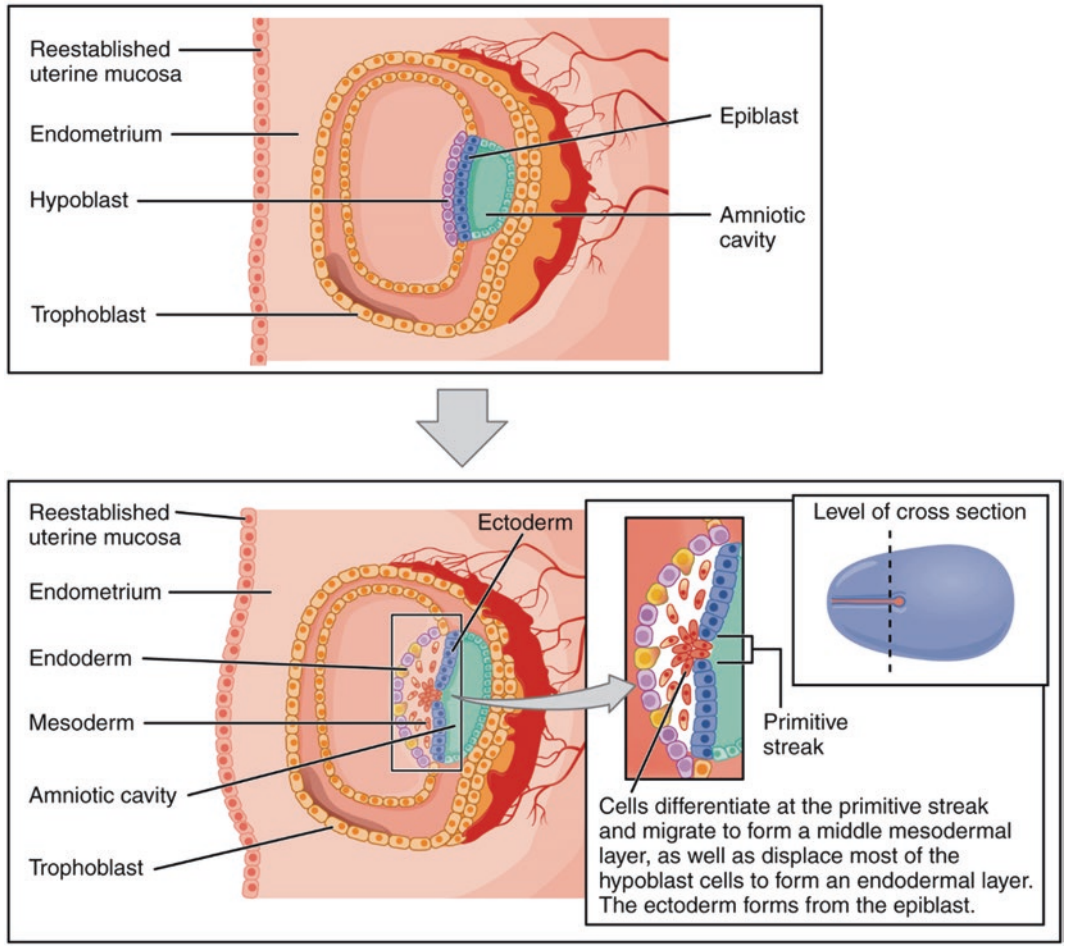

Fig. 1 Germ Layers. Formation of the three primary germ layers occurs during the first 2 weeks of development. The embryo at this stage is only a few millimeters in length [2]

medial, intermediate and lateral plate mesoderm [4–6]. Both visceral and parietal pleurae derive from the lateral plate mesoderm which splits into two layers (1) the somatopleuric mesoderm forming parietal pleura and (2) the splanchnopleuric mesoderm of visceral pleura [4].

Trilaminar human embryo. Each of these germ layers goes on to form in embryo special structures and organs. ***Endoderm*** creates the epithelial lining of lungs, gastrointestinal tract, liver and pancreas. ***Mesoderm*** cells convert into the connective tissue, muscles, skeleton, blood, heart, vessels, and kidneys. ***Ectoderm*** goes on to develop into the epidermis, hair, nails, central and peripheral nervous systems, and sensory organs (Fig. 2) [2].

After gastrulation, embryonic cells from all three above layers start to migrate and separate in the cell lineages with ***organogenesis*** [2] that theoretically comprises the first 8 weeks of gestation. In same time, ***gastrulation*** is also followed by ***neurulation*** in which ectoderm gives

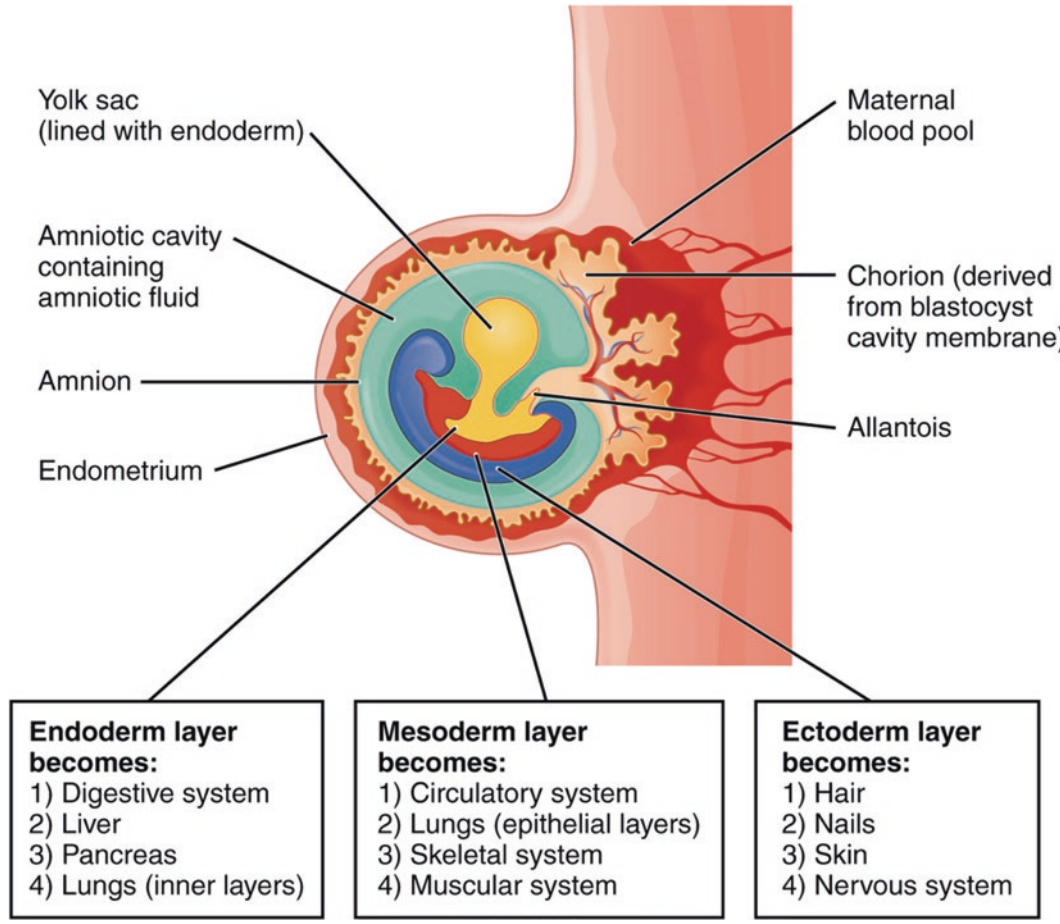

Fig. 2 Fates of Germ Layers in Embryo. Following gastrulation of the embryo in the third week, embryonic cells of the ectoderm, mesoderm, and endoderm begin to migrate and differentiate into the cell lineages that will give rise to mature organs and organ systems in the infant [2]

rise to elementary structures of the central nervous system. In fact, neural plate is **folding** itself to create the neural tube and neural crest [2].

Folding of the embryo (Fig. 3) [2]. Embryo folding is followed by the widening of head fold, and the primitive heart together with the future pericardial space get in the ventral part of foregut. Initially, the septum transversum is located cranial to the pericardial cavity, but at the end of embryogenesis becomes trapped between heart and isthmus of the yolk sac [7]. As well, the human embryo elongates craniocaudally and folds laterally. Dorsal part of the yolk sac, composed of endoderm, is compressed by the lateral folding of embryo and is incorporated as a rim during the ***fourth week*** (Fig. 3) [2, 4]. After folding, the embryo gets a tube-shaped form.

Week 4.

The ***extraembryonic coelom*** comprises the yolk sac, amniotic cavity and chorionic cavity. The ***intraembryonic coelom*** (IEC, the coelomic cavity) develops as the space localized in lateral plate mesoderm. It will later develop into the 3 main body cavities: pleural, pericardial and peritoneal.

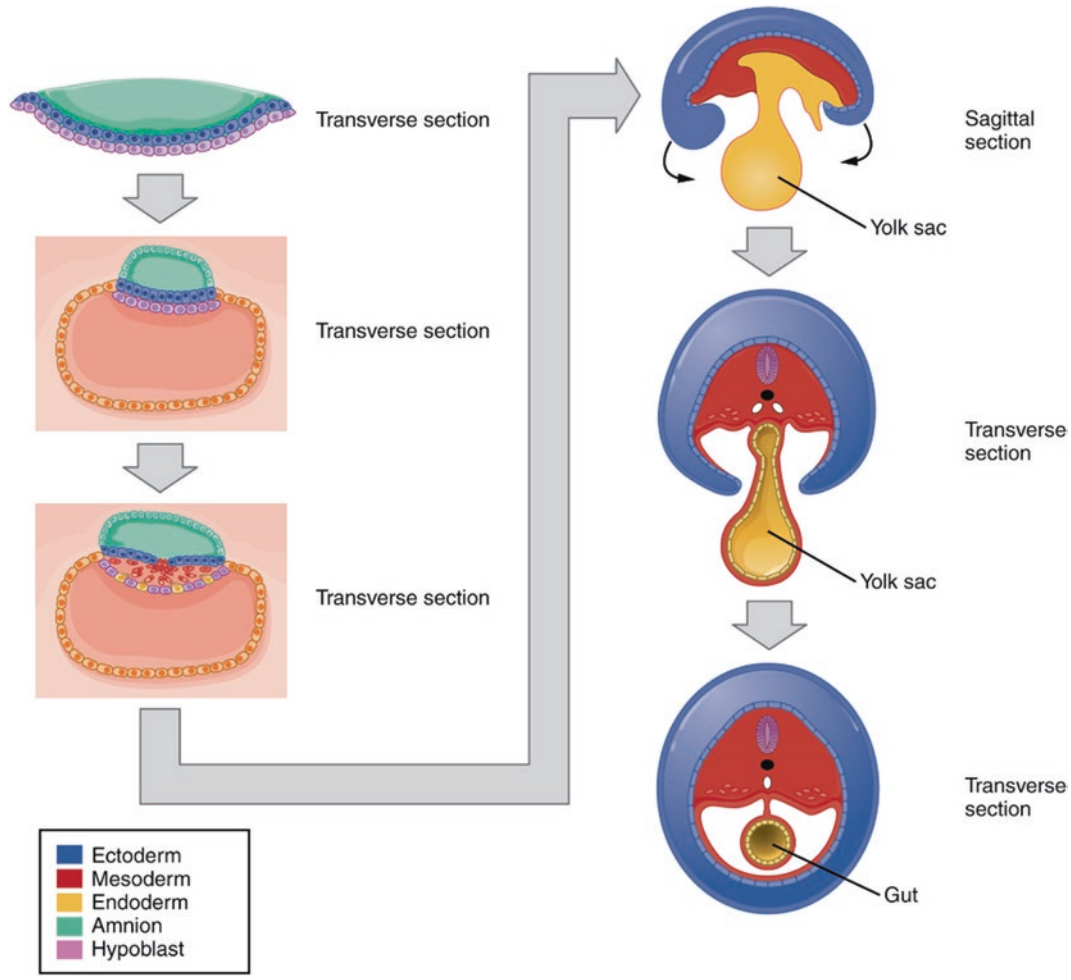

Fig. 3 Embryonic **Folding**. Embryonic folding converts a flat sheet of cells into a hollow, tube-like structure [2]

Development of pleura in the human embryo begins around ***week 4*** (stages 8 to 10; Carnegie 23–28 days). *Starting with the* ***4th week*** when ***body folding*** happens, the two pleural cavities are forming from the intraembryonic coelum (IEC, coelum) that arises from the separation of the *lateral plate mesoderm* on each side of the embryo in two layers: the parietal (somatic, somatopleuric) mesoderm and the visceral (splanchnic, splanchnopleuric) mesoderm [4, 5]. Therefore, the space between somatopleure and splanchnopleure is the intraembryonic coelum (IEC) that serves as the containment space of the viscera [8].

During 4 week, the lateral plate mesoderm develops tiny spaces which join together forming intraembryonic coelum (IEC) that is a large horseshoe-shaped area or U-shaped cavity or coelomic with the bend situated anteriorly (Fig. 4) [6, 7, 9].

Before folding, the intraembryonic coelum (IEC) is placed caudal to the septum transversum and partially encircles the future head end of embryo [9]. The septum transversum appears on the third week (day 22) and comprises a layer of mesoderm that develops as half-round structure rostral to the primitive heart (Fig. 5) [7]. As

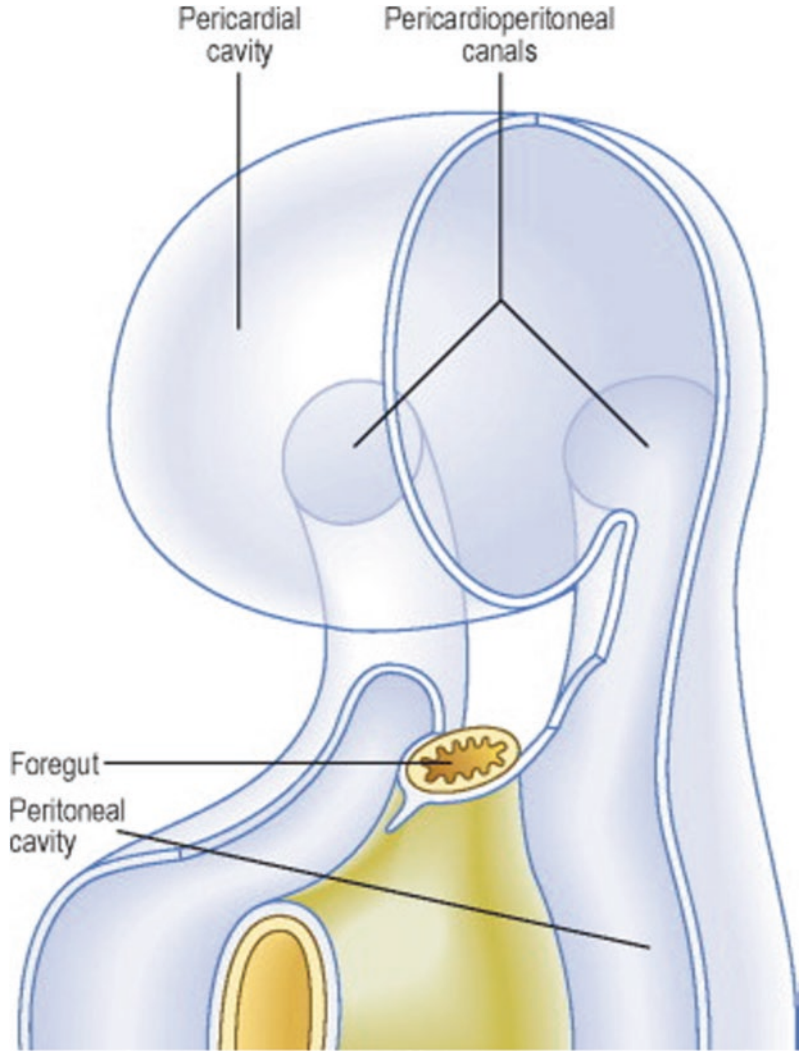

Fig. 4 The ventrolateral view of the intra-embryonic coelom in a **4-week embryo** with surrounding tissues removed. See Ref. [7] **with permission**

stated above, folding of human embryo causes the anterior relocation of lateral parts of mesoderm on the median line to incorporate the yolk sac with creation of IEC [10]. This relocation of mesoderm during folding separates the lateral mesoderm into somatic (parietal) layer and splanchnic (visceral) layer, both covering the IEC [10].

As described before, IEC (coelum, intraembryonic space IEC) is a U-shaped cavity divided into three regions (1) ***pericardial coelum*** represented by dilated bend of the U-shaped cavity, that at 3 weeks overlies the cardiogenic tube; and (2) ***R and L coelomic ducts*** which lie alongside the oropharyngeal membrane and prechordal plate. Both coelomic ducts represent the origin of pleural and upper abdominal cavities [6, 9].

By the fourth week (stage 10 or 28 days) the cranial end of IEC comprises a central part (the pericardial cavity), and two lateral narrow canals (the pericardioperitoneal canals). Both

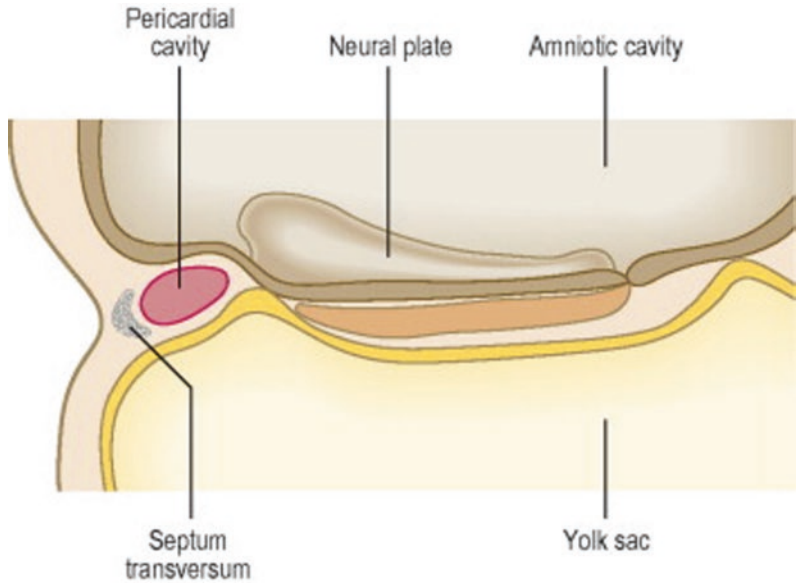

Fig. 5 Sagittal section of a **3-week** embryo showing the position of the septum transversum rostral to the pericardial cavity. From Ref. [7] **with permission**

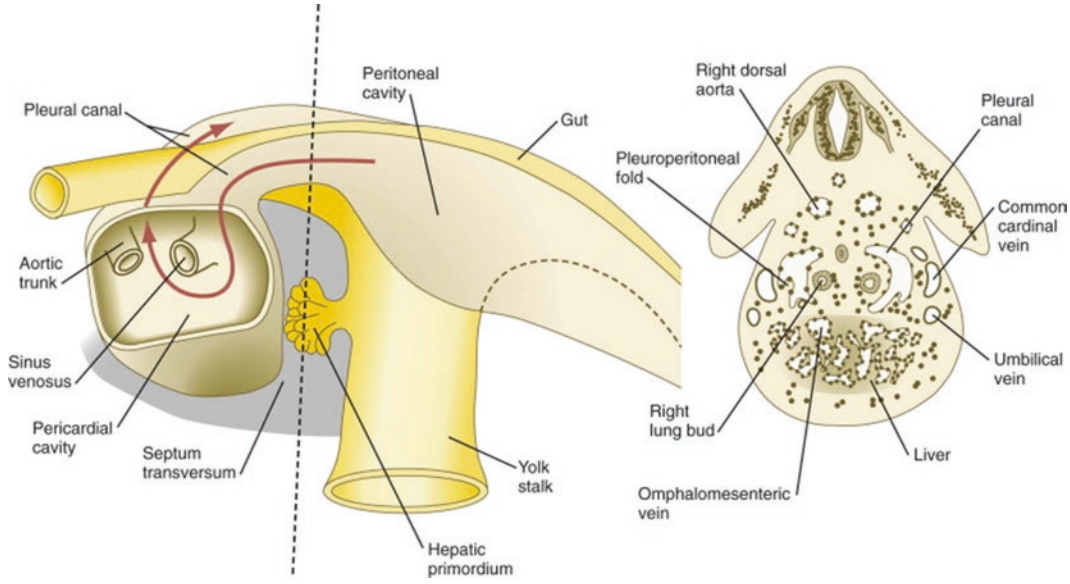

Fig. 6 Relationships among the pericardial cavity, pleural canals, and peritoneal cavity. [11]. The red arrow run from the left pleural cavity into the pericardial cavity and then into the right pleural canal. On the left, the dashed line corresponds to the separation on the right. See Ref. [11] **with permission**

pericardioperitoneal canals join the IEC (future peritoneal cavity) with the pericardial cavity (Fig. 6) [11].

Pleuroperitoneal membranes (or folds) represents an early embryonic membrane that forms inferiorly at the ***septum transversum*** to separate

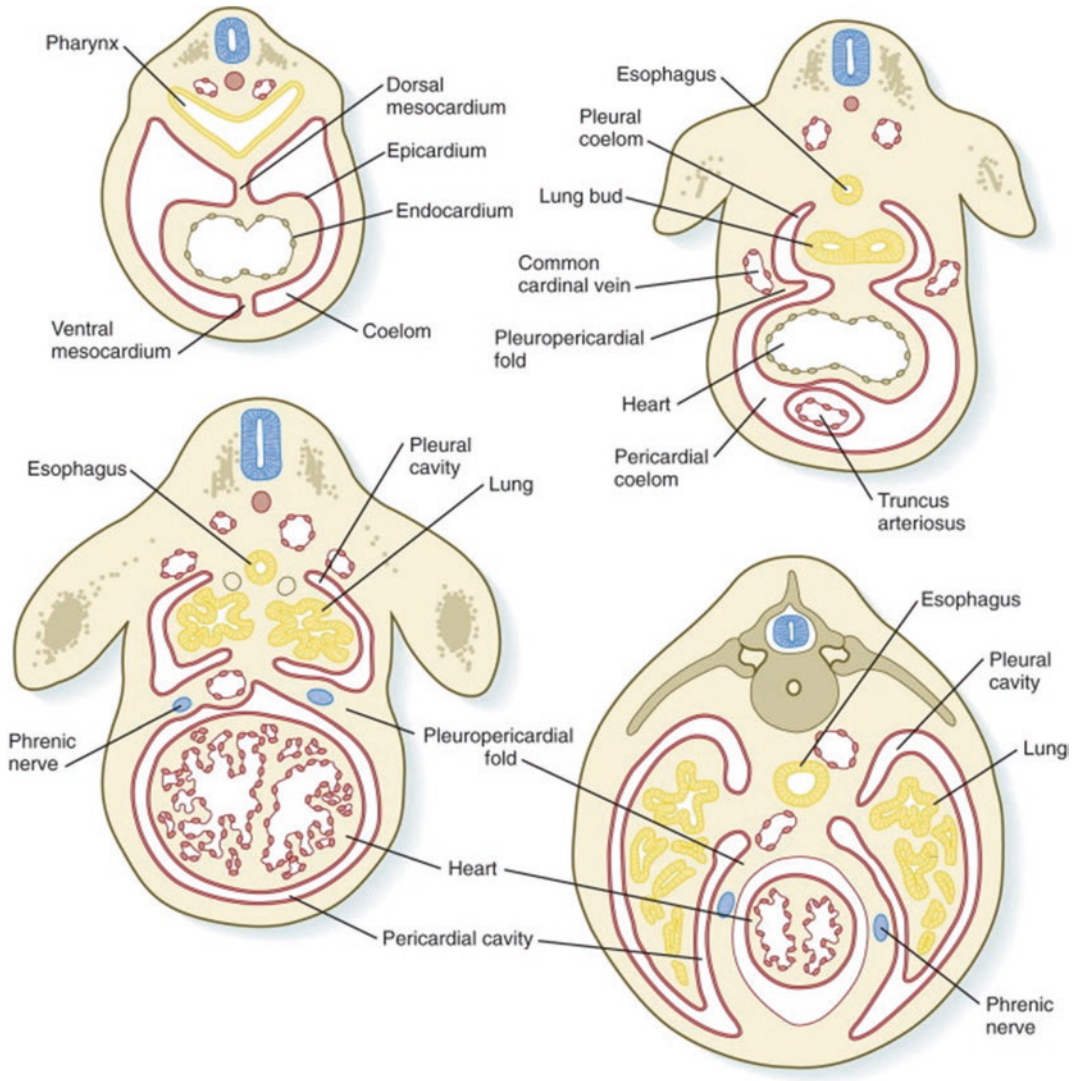

Fig. 7 Development of the **pleuropericardial folds**. Adapted from Carlson [11] **with permission**

peritoneal cavity from pleural cavity. It is formed by mesenchyme which contains both the cardinal vein and phrenic nerve [12]. By time, as these pleuropericardial folds bend toward the median line of the thoracic part of IEC, protrude into the dorsolateral wall of coelom and, pass in the sinus venosus of heart (Fig. 7) [11].

With folding of the embryo, phrenic nerves run down at the level of lower thoracic vertebrae [11]. The route of phrenic nerve within the fibrous pericardium represents the initial association with pleuropericardial folds [11].

Pericardioperitoneal canals connect the developing pericardial and peritoneal cavities. Further, these canals enlarge into pleural cavities along side the developing lungs from lungs bud [6]. Subsequently, the lung buds grow into the medial wall of pericardioperitoneal canals or ***primitive pleural cavities*** [12]. The free ends of ***pleuropericardial membranes*** extend dorsally, approach each other and finally fuse with each other and with the root of lungs, separating the pericardial cavity from the pleural cavities [12]. Because of large size of the right common

cardinal vein, the membrane on right side is larger, and the right opening closes slightly earlier than the left one [12].

Week 5.

At the beginning of the ***fifth week***, the lung buds grow into the medial wall of the pericardioperitoneal canals or primitive pleural cavities [12]. These cavities expand ventrally around the heart by splitting the mesenchyme of body wall [12]. Along with their growing, the lung buds (anlage) enlarge the pericardioperitoneal canals to develop into the pleural cavity.

Shortly, as the lung buds develop into the mesoderm of body wall, the pleuroperitoneal folds extend from caudal ends of the paired pleural canals [11]. These membranes grow ventrally to fuse with septum transversum, thus sealing off the pericardioperitoneal canals [9]. The left pericardioperitoneal canal is larger than the right and closes later [12] being significant in the possible developing of congenital diaphragmatic hernias [9].

Pleuroperitoneal membranes develops and will close ventrally the pericardioperitoneal canal. The pericardioperitoneal membranes that close these canals are called pleuroperitoneal membranes because they do not contact the septum transversum until after the pericardial sac is formed; thus, after they fuse with septum transversum, they separate the definitive pleural cavities from the peritoneal cavity [9]. During development, the pleuroperitoneal folds develop with their bulging in the pleural canals, and finally obliterate the pleural canals by joining with the septum transversum and the mesentery of the esophagus (Fig. 8) [11].

Week 6.

During week 6, heart and lungs go down into thorax with closure of the pleuroperitoneal foramen.

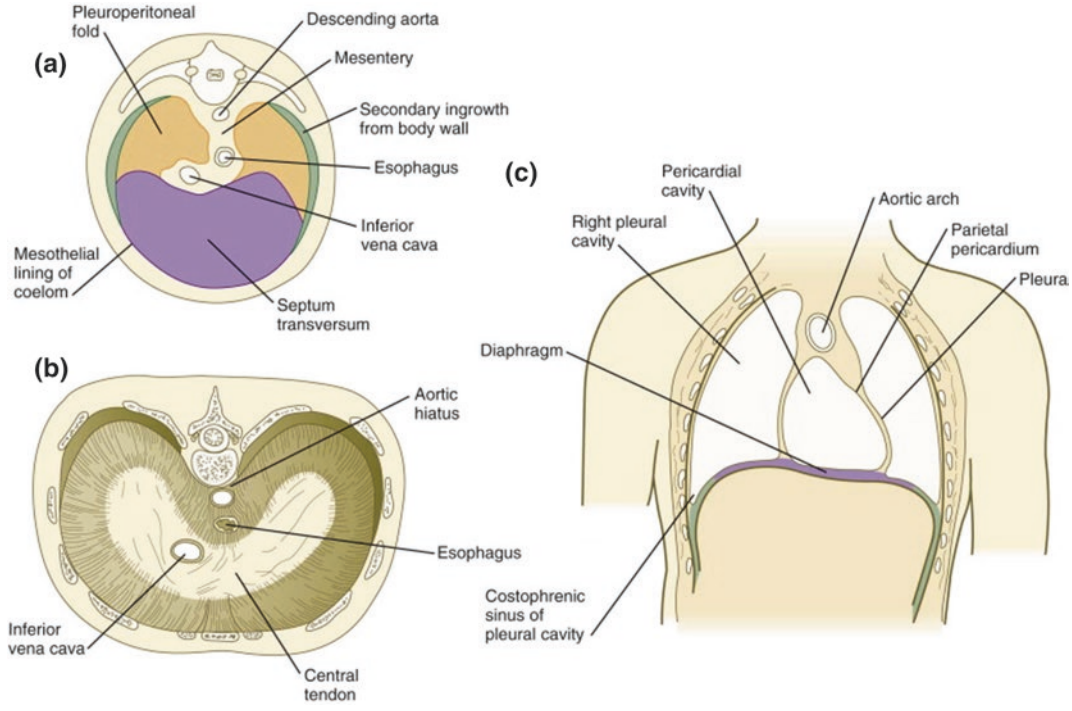

Fig. 8 Stages in the formation of the diaphragm. A, Components making up the embryonic diaphragm. B, Adult diaphragm as seen from the thoracic side. C, Frontal section showing relations of the diaphragm to the pleural and pericardial cavities. See Ref. [11] **with permission**

Week 7.
By the end of ***week 7***, liver growth blocks the fall of heart and lungs, and the fusion of pleuroperitoneal membranes with the septum transversum is completely, with partition of IEC into thoracic and abdominal cavities [9]. It has to be underlined that after fusion of the pleuroperitoneal membranes with the septum transversum, the septum transversum develop into the central tendon of the diaphragm, while the pleuroperitoneal membranes turn into the musculature of the diaphragm. By the end of the seven weeks, mesoderm develops the parietal and visceral pleura [9]. The visceral pleura begins the separation of heart from the lungs and isolate the lungs into lobes [9].

By the end of embryogenesis, the embryo has about 3 cm (1.2 in) from crown to rump and weighs approximately 8 g (0.25 oz) (Fig. 9) [2]. At the end of the embryonic period appears the first breathing movement [13].

Pleural Histology

Surfaces of the thoracic cavity are covered by pleura that is a thin ***serous membrane*** formed from a layer of squamous mesothelial cells tightly attached by a network of dense connective tissue containing elastic and collagenous fibers (Fig. 10) [14, 15]. Therefore, this submesothelial layer comprises dense connective tissues, blood vessels, and lymphatics [16].

Specifically, lungs and adjacent structures, are covered by the **visceral pleura** (inner membrane) via blood vessels, bronchi and nerves

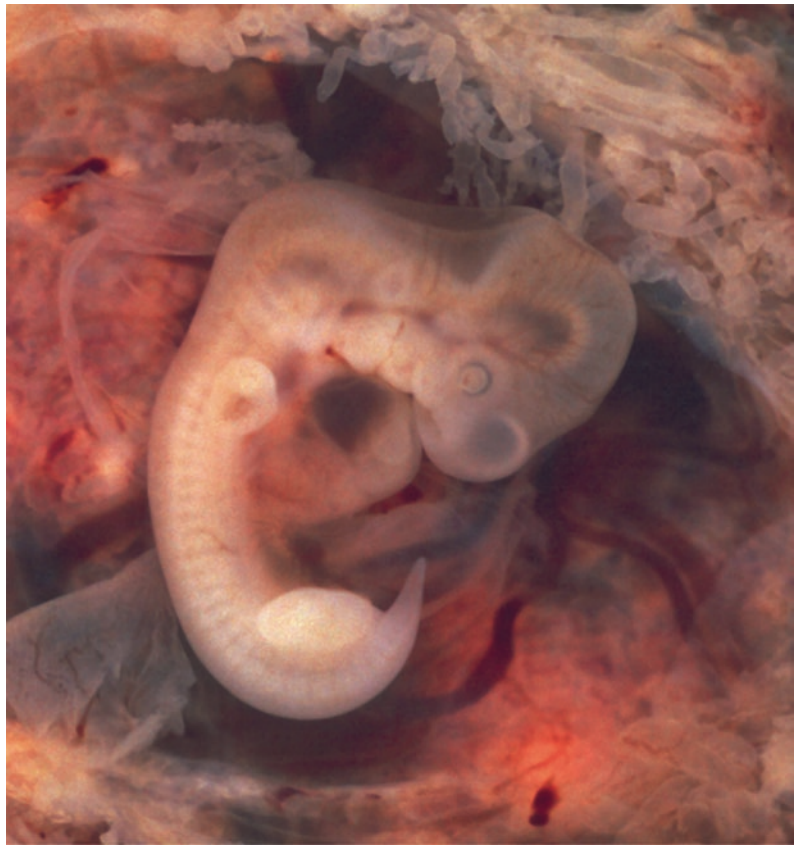

Fig. 9 Embryo at 7 Weeks. An embryo at the end of **7 weeks** of development is only 10 mm in length, but its developing eyes, limb buds, and tail are already visible. (This embryo was derived from an ectopic pregnancy.) (credit: Ed Uthman) [2]

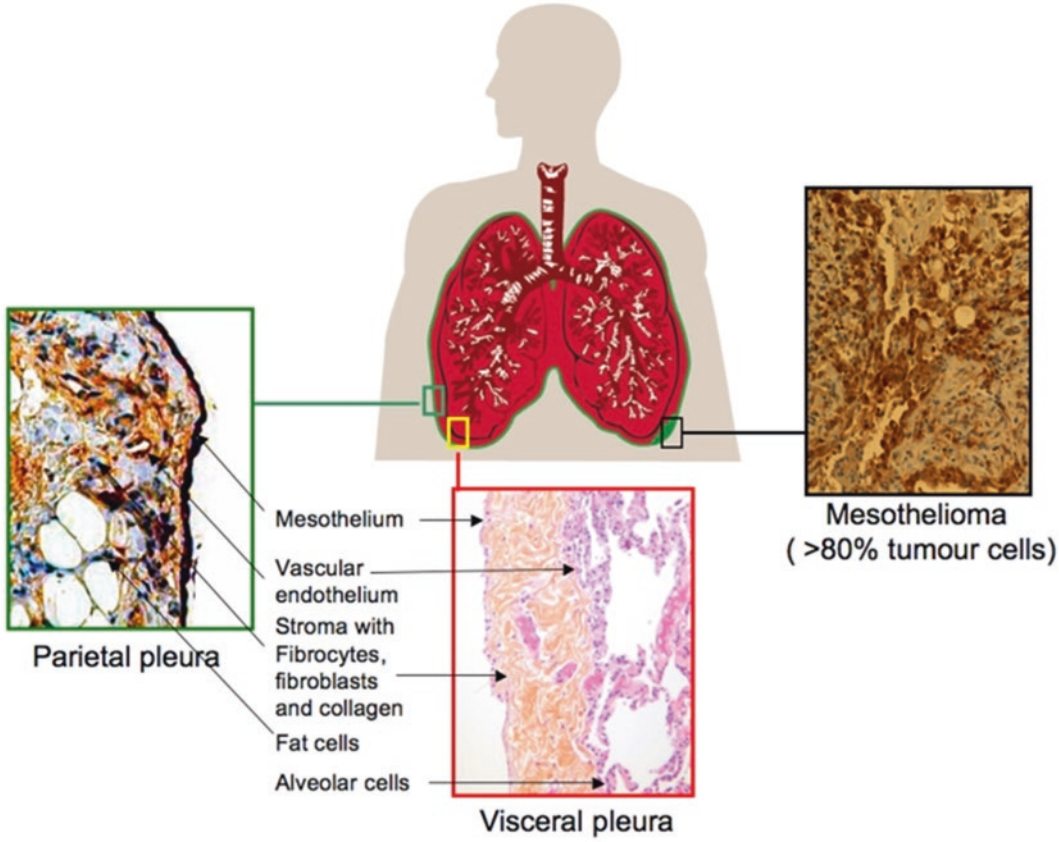

Fig. 10 Schematic presentation of mesothelioma, the parietal and visceral pleura. Representative histology showing the most abundant cell types [15]

[17], while the **parietal pleura** (outer membrane) covers the inside of rib cage, diaphragm, and mediastinum [14]. Pulmonary pleural width in mammals is from 20 to 80 μm [16].

Initialy, both pleural sheets have been described as a similar histological structure consisting of 5 layers: mesothelial layer, submesothelial (inner connective) layer, superficial fibroelastic, subpleural (external connective), and deep fibroelastic layer [18].

However, ***visceral pleura*** has five layers such as (1) mesothelial cells without a basement membrane, (2) a submesothelial layer of loose connective tissue; (3) elastic layer; (4) the loose (interstitial) connective tissue comprising collagen, blood vessels, and lymphatics; and (5) elastic fibers and fibrous tissue tightly attached with the lung [19]. Therefore, the ***visceral pleura*** is adherent to lungs through the last two layers. It covers the entire surface of lungs, infiltrating into fissures between the lobes, tightly attached to the pulmonary fibroelastic network, with a special functional role in the respiratory mechanics (with uniform distribution of the mechanical forces on the pulmonary parenchyma). When the fibroelastic connections between the visceral pleura and the alveolar walls breakdown, the underlying blebs appear to be involved in the occurrence of primary spontaneous pneumothorax [20].

Parietal pleura has some differences from visceral pleura. It is made up from only one layer of cuboidal mesothelial cells sustained by loose connective tissue that comprises a single elastic layer with blood vessels and lymphatics, with a thickness from 1 to 4 μm [21].

Both parietal pleura and chest wall adipose tissue interdigitates within a layer of dense collagen tissue forming the endothoracic fascia that merges with either rib periosteum or skeletal muscle [19].

The parietal pleural effusion is thicker than the diaphragmatic and mediastinal parietal pleura. It has a resistance structure in the deep fibroelastic plane, known as the "Luschka endothoracic fascia". This plays an important role in pleural effusions, allowing for extrapleural decortication when the plane of decortication is within the connective subpleural tissue (the endothoracic fascia remains adherent to the chest wall). Due to the absence of endothoracic fascia for diaphragmatic and mediastinal pleura, which are thinner and intimately adherent to the underlying structures, decortication is not possible. Moreover, parietal pleura of ribs presents the 6th histologically layer named the subfascial layer, through which the pleura, via the endothoracic fascia, adheres to the periosteum of ribs and the fascia of intercostal muscles. Parietal decortication achieved in this plane is called extrafascial decortication.

Parietal pleura is distinguished from visceral pleura by the presence of stomas and sensory innervation [21]. Parietal stomas have the diameter of 2–12 μm with caudal location [21]. With inspiratory maneuvers, stomas may increase tenfold in size [21].

Each stoma is an opening that exists between the mesothelial cells on the parietal pleura [22]. Characteristically, these stoma (or stomata) are small holes with diameter of 1–6 μm and are localized between mesothelial cells on the parietal pleura, with the role to filter and remove excessive pleural fluid with its proteins and cells into the parietal pleural lymphatics (Fig. 11) [10, 22, 23]. Primarily, role of stomas is to drain fluid collection by lymphatic glands. The submesothelial layer of parietal pleura contains

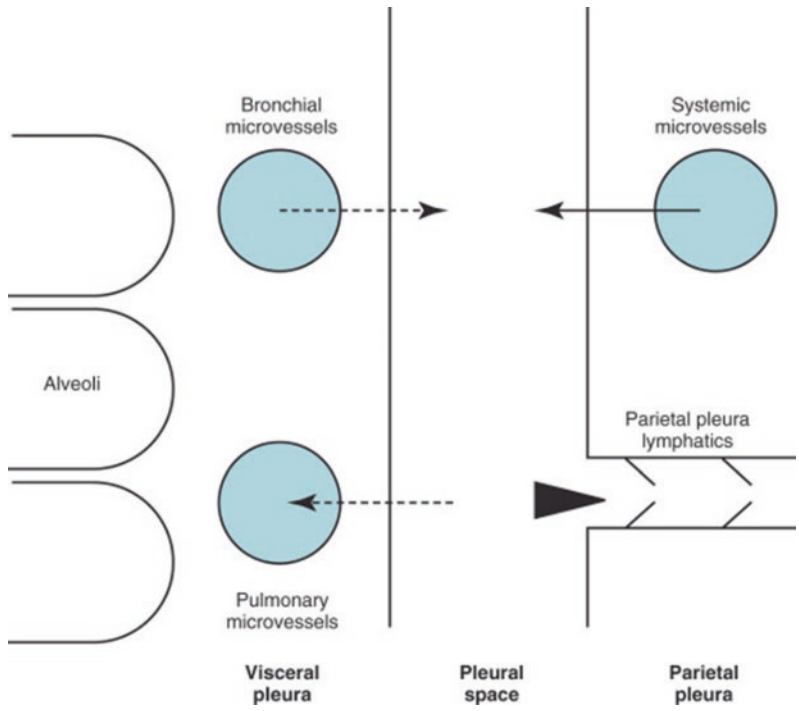

Fig. 11 Schematic diagram of normal filtration and resorption of fluid in pleural space. Solid arrow shows filtration of fluid from parietal pleural microvessels into pleural space. Arrowhead indicates removal of fluid through stomata and into parietal pleural lymphatics. Dashed arrows indicate a minor role for filtration and resorption of fluid by visceral pleural microvessels. (Modified from 23). From [22] **with permission**

lymphatic vessels. Whereas anterior parietal pleura has drainage into the internal intercostal lymph nodes, the posterior parietal pleura has drainage into the lymph nodes placed near the internal thoracic artery [21].

To sum up, stomata from parietal pleura are localized in the caudal intercostal spaces, diaphragm and in parietal pleura of ventral mediastinum and caudal mediastinum [24–26]. It has to be underlined that stomata are distributed as "Kampmeier foci" which are complexes of specific mesothelial cells and macrophages (histiocytes, lymphocytes, other mononuclear cells and plasma cells) surrounding a lymphatic/vascular vessel [27, 28].

Topography of the Pleura

The pleura consists of two serous membranes, one covering the lung (visceral pleura) and one that tapers the inside of chest wall (parietal pleura). Both pleural sheets slide between them, facilitating the pulmonary movements during the breathing phases. They continue with each other at the level of the pulmonary hilum, where they form a pleural reflection that extends to the diaphragm, forming the triangular ligament. Between two pleural sheets is defined the pleural cavity (pleural space), which is normally a virtual space containing only a small amount of lubricating liquid: 0.1–0.2 ml/kg and 10 μm thickness.

Visceral pleura. It is very adherent to the surface of lung, penetrating into the fissures. Inflammation of the pleura of this level (interlobular pleurisy, interlobitis), pathological adhesions may occur between the interlobar faces of visceral pleura.

Visceral pleura covers the whole of the lung, except for a small portion of the pulmonary hilum where is forming the line of reflection to the parietal sheet. Reflection of the visceral pleura towards the parietal pleura, located lower than the pulmonary hilum, participates in the formation of the triangular ligament (an important hallmark for discovery of the lower pulmonary vein).

Parietal pleura. Depending on the walls it wraps, parietal pleura it is called: costal pleura, diaphragmatic pleura, mediastinal plexus and apical pleura (cervical pleura, pleural dome or cupula). The costal and apical pleura are thicker than diaphragmatic pleura. They can be taken off the chest wall (extrapleural and extrafascial decortications).

The costal pleura surrounds the inner surface of rib cage. It covers the front of sternum, the thorax transversal muscle, the internal thoracic arteries, the rib cartilages, the intercostal ribs and spaces, the sympathetic paravertebral chain, and the anterior costovertebral ligaments. It continues to anterior and posterior with the mediastinal pleura. Along the lines of reflection, two pleural recesses or sinuses are formed the anterior and posterior costomediastinal recesses. The costal pleura penetrates into the lower part of deep space between wall and diaphragm to form the costodiafragmatic recess along the reflex line to the diaphragmatic pleura. At the tip of the lung, the costal pleura continues with mediastinal pleura, making the pleural cupula or dome.

Mediastinal pleura adheres to the connective tissue of mediastinum (note the absence of the cleavage plan at this level). Above the lung hilum, pleura has a sagittal direction, from the sternum to the spine. At hilum level, it reflects on it to continue with the visceral pleura. Under hilum, mediastinal pleura is also continued with the visceral sheet, in the form of a triangular structure made up of two sheets and disposed in the frontal plane. It goes down to the diaphragm and binds to the fibrous pericardium of medial face of lung, taking part in the formation of pulmonary ligament (triangular ligament).

Diaphragmatic pleura covers the upper face of diaphragm, being adherent to it (note no cleavage plan at this level).

Cervical (cupula) pleura corresponds to the cervical portion of parietal pleura. At the level of upper thoracic aperture, the parietal pleura extends out with 2–3 cm like a dome or cupula due to the diagonal level [29]. Its convex face is constituted as a fibrous membrane, the suprapleural membrane, which is an extension of

endothoracic fascia, through which apical pleura adheres to superior thoracic aperture. Therefore, from endothoracic fascia runs off suprapleuralis membrane which reinforces free lateral part of pleural dome. Also, strong tracts of connective tissue fix the suprapleuralis membrane with the first rib. The pleurovertebral ligament comes from the deep neck fascia at the level C6–C7, with attachment of the pleural dome and preventing its collapse during inspiration [29].

It has to be underlined that the ***anterior part of pleural dome*** shows relations with the neurovascular bundle at the base of the neck, structured in three anatomical planes: (1) deep—the arterial plane (subclavian artery and its collateral branches), (2) superficially—the venous plan (subclavian vein and its tributaries), in the (3) middle, between the artery and the vein of subclavia—the nervous plan (vagus nerve with recurrent right laryngeal nerve, ansa subclavia or Vieussens' ansa and phrenic nerve).

The ***posterior part of pleural dome*** corresponds to the neck of first rib. At this level the pleura is depressed to form the supraretropleural fossa (Sebileau's fossette, 1892). The triangular space bounded between pleural cupula and neck of first rib contains the stellar ganglion. Also posteriorly, the pleural cupula presents relations with lower root of the brachial plexus (C8-T1).

On the convex face of apical pleura, the 'pleural cupula ligament' has a ligament component and a muscular component (anterior and middle scalenes). Sectioning of this ligament with decortication and lowering of the lung peak, is called extrapleural or phascial apical dissection or apicolysis—a procedure previously used for treating pulmonary tuberculosis.

Pleural recesses form at the site of reflection of parietal pleura from one wall to another. There are five pleural recesses: (1) anterior costomediastinal (retrosternal) recess, (2) posterior costomediastinal recess, (3) superior costomediastinal recess, (4) mediastinodiaphragmatic recess, and (5) costodiaphragmatic recess (costophrenic recess or phrenicocostal sinus) (inferior). Usually, pleural effusions appear into the costodiaphragmatic recess.

Costodiaphragmatic recess (Fig. 12) is the most important because between it and the diaphragm insert there is a costodiaphragmatic

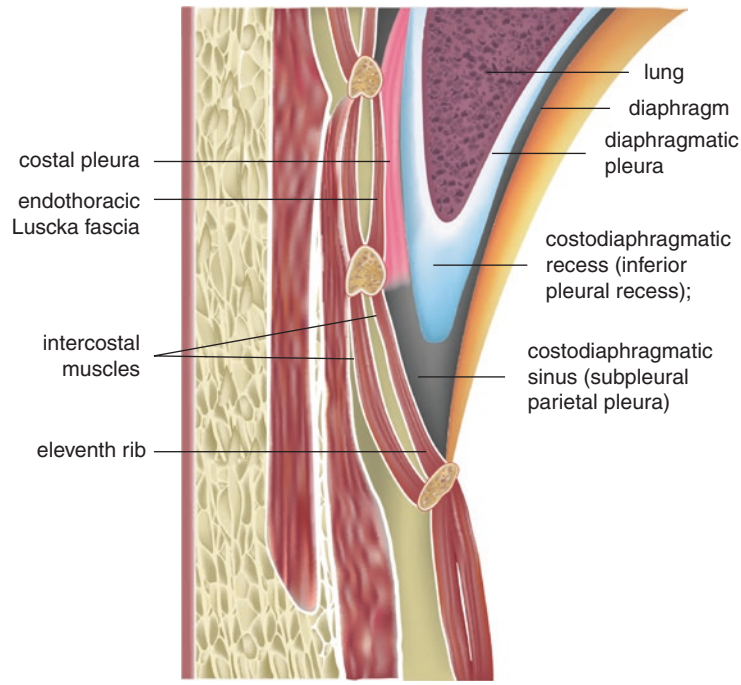

Fig. 12 Costodiaphragmatic (inferior pleural) recess—frontal plane section on mean axillary line

sinus through which the transthoracic approach of subdiaphragmatic space is possible without opening the pleural cavity.

Vascularization of the Pleura

Visceral pleura receives blood from both arterial system such as pulmonary and systemic (through the bronchial arteries) circulations, while venous drainage is done in the pulmonary veins.

Parietal pleura receives blood only from the systemic arteries (1) costal pleura from the intercostal arteries and internal mammary arteries, (2) mediastinal pleura from bronchial arteries, superior diaphragmatic artery and internal mammary arteries. The arterial blood of pleural dome comes from the subclavian artery. The venous blood of parietal pleura is drained through peribronchial veins directly into the superior vena cava.

The lymphatic drainage of the ***visceral pleura*** is through a large network of subpleural lymph capillaries (more abundant in the lower lobes) into the peribronchial and interlobular deep veins.

Riquet [30] has described direct lymphatic connections between subpleural network and mediastinal nodes (in 22–25% of the studied cases). These underlying connections are more common in upper lobes of lungs [20].

Lymphatic drainage of parietal pleura is made by the direct communication that exists between the pleural stoma from pleural cavity and the lymphatic channels of parietal pleura.

These pleural lymphatic channels run parallel to the ribs to reach the internal mammary nodes and intercostal lymphatic nodes [25]. Whereas anterior parietal pleura has drainage into the internal intercostal lymph nodes, posterior parietal pleura has drainage into the lymph nodes placed near the internal thoracic artery [21].

Drainage of the diaphragmatic pleura is made both to retrosternal and mediastinal lymph nodes and to celiac lymph nodes of the abdomen.

Pleura Innervation

Visceral pleura is devoided of somatic innervation. Parietal pleura receives both somatic and visceral nerve fibers (sympathetic and parasympathetic) via intercostal nerves. The diaphragmatic pleura also receives fibers from the phrenic nerve.

Surgical Considerations on Anatomy of the Pleura

Apical pleura corresponds to cervical portion of parietal pleura and constitutes pleural cupula or pleural dome. Apical pleura adheres to upper thoracic aperture and is located extrathoracically at the base of neck, occupying the supraclavicular region, presenting with the vascular nerve elements at base of neck, structured in three anatomical planes: (1) profound—arterial plane (the subclavian artery and its collateral branches), (2) superficial—the venous plan (the subclavian vein and its tributaries), (3) in the middle, between the artery and vein of the subclavia—the nervous plane (the vagus nerve with the recurrent right, the Vieussens and the phrenic nerve). Anterior ratio of apical plexus to venous vascular plane (the most superficial plane) containing the internal subclavian and jugular veins should be considered by the anesthesiologist when inserting a central venous catheter in the subclinical veins or internal jugular veins due to the risk of pleural perforation apical with the occurrence of pneumothorax that appears as a complication of this maneuver.

The posterior thoracic projection of costodiaphragmatic recess and thus of parietal costodiaphragmatic pleura reaches bilaterally at the level of the 12th rib on the paravertebral line, having the same projection area with the upper kidney pole. In kidney surgery, a longer incision can cause the opening of these recesses as pneumothorax. There is also a transthoracic approach to the renal pole through the resection of the 12th rib.

There are patients with upper diaphragm located (such as deformities of the spine, obese, diaphragm upward located postoperatively, diaphragmatic relaxation) in which the surgical approach of pleural cavity such as thoracotomy or placement of thoracoscopic trocars or simple pleural drainage performed for various pathologies, may cause damage to the diaphragm or organ located below the diaphragm (liver, spleen, left colic (spleen) flexure). Therefore, in these patients, chest incisions should be avoided or the transthoracic ultrasound should be used.

Since anterior chest projection of the costomediastinal pleural recession is bilateral, at the retrosternal level, there is a risk of opening the pleural space with occurrence of pneumothorax during median sternotomy or anterior parasternal mediastinotomy, pathways for various pathologies. The onset of this complication requires pleural drainage.

Anterior chest projection of lower left anterior costomediastinal recess overlaps with the anterior projection of fibrous pericardium. This must be taken into account during various surgical techniques of pericardial cavity, pericardiocentesis, pericardiotomy by subxiphoid or left paraxifoid approach, due to the risk of simultaneous opening and left pleural space with the occurrence of pneumothorax.

The tight report of diaphragmatic parietal pleura with the diaphragm's upper face (absence of the cleavage plan at this level) should be considered during abdominal surgery performed at the diaphragmatic pillars (surgical cure of hiatal hernias) because there is a risk of opening the pleural space with pneumothorax (favored by the use of pressurized gas in laparoscopic surgery).

Self-study

1. Which statement is/are true:

   a. The embryonic period extends from fertilization to week 9.
   b. Pleural cavity is created between the 4–7 weeks of embryologic development.
   c. Both visceral and parietal pleurae derive from the lateral plate mesoderm.
   d. Development of pleura in the human embryo begins around *week 4*.

Answers

1. Which statement is/are true:

   a. CORRECT
   b. CORRECT
   c. CORRECT
   d. CORRECT.

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Classical and Minimally Invasive Approaches and Surgical Techniques for Malignant Pleural Effusions

Claudiu E. Nistor, Adrian Ciuche, and Ecaterina Bontaș

Key Points

- Pleural fluid labelled as transudates generally reflect a systemic disorder, while exudates signify usually the existence of a local pathology (pleuro-pulmonary pathology).
- Type I malignant pleural effusion occurs as a result of the neoplastic invasion of the pleura by a primary or secondary tumor.
- Type II malignant pleural effusions (paraneoplastic pleural effusion) may occur in patients with confirmed cancers when the neoplasic process does not involve the pleura.
- Malignant PE have poor prognosis.

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Definitions

The pleural cavity normally contains a small amount of liquid (about 10 ml) on either side [1]. Pleural effusion (PE) occurs when there is an imbalance between the production rate and the absorption rate, resulting in excess of pleural fluid accumulation.

In 1972, Light and his collaborators classically divided the pleural effusion (PE) into two broad categories: transudates and exudates (Table 1) [2–4], while pointing out the essential difference between them: transudates generally reflect a systemic disorder, while exudates signify usually the existence of a local pathology (pleuro-pulmonary pathology).

According to Moghissi, there are two types of PE associated with neoplastic disease: type I (true malignant PE) and type II (paraneoplastic PE) [5].

Type I malignant PE occurs as a result of the neoplastic invasion of the pleura by a primary or secondary tumor, the diagnosis being a cyto-histological one consisting in the identification of malignant cells in the pleural fluid or in the pleural biopsy material.

Type II malignant PE (paraneoplastic PE) may occur in patients with confirmed cancers when the neoplasic process does not involve the pleura (absence of neoplastic cells in both pleural fluid and pleural biopsy fragments).

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Table 1 Diagnostic criteria or Light's criteria for exudates and transudates [2–4]

Lights criteria	Transudate/Transudative	Exudate
Pleural fluid proteins	<3 g/dL	>3 g/dL
Pleural fluid proteins/plasma proteins	<0.5	>0.5
Pleural fluid LDH	<200 U/L	>200 U/L
		>2/3 × upper reference limit for plasma LDH
Pleural fluid LDH/Plasma LDH	<0.6	>0.6

Malignant PE may represent from 27 to 61% of total PE cases [5]. Furthermore, malignant PE is the second cause of PE after parapneumonic inflammation [6]. It seems that the most common cancers associated with malignant PE are lung cancer, breast cancer and lymphoma [7]. Also, lung cancer, lymphoma and digestive cancers are the first involved in the development of malignant PE in males, while women have PE due to breast tumors, genital tract (usually ovary), and lung cancers [8]. Generally the outcome of malignant PE is poor.

Pathogenesis

To begin with, PE occurs due to the imbalance between the mechanisms of production and absorption of about 5–10 liters of fluid that crosses the pleural cavity within 24 hours, with the excess of 5–20 ml of fluid that is normally present in pleural space at any time [9].

There are differences in the pathogenesis of the two types of malignant PE.

In type I, the most likely cause for PE is the increase of pleural capillary permeability in the inflammatory response generated by pleural tumor invasion. This mechanism leads to extravasation of rich protein (exudate) in pleural fluid [6]. The mechanism by which pleural metastases increase the permeability of pleural capillaries is not fully known. There are studies that highlight the importance of vascular endothelial growth factor (VEGF) production by tumor cells [6]. VEGF is one of the most potent known agents for increasing vascular permeability [10]. The VEGF level in pleural fluid is much higher in malignant PE than inflammatory PE. In neoplastic PE, the VEGF concentration is higher in haemorrhagic PE than in non-haemorrhagic PE [11, 12].

The large amount of pleural fluid accumulation is also due to the blockage of the lymphatic drainage of the pleural space by the neoplastic process. Lymphatic blockage can occur at any level, from the parietal pleura to the mediastinal lymph nodes and internal mammary lymph nodes. There are studies which demonstrate that impaired pleural lymphatic drainage is probably the most important mechanism responsible for the accumulation of large volumes of fluid in cancer [13, 14].

In the occurrence of paraneoplastic PE, the following etiologies of disruption of the production-absorption equilibrium are involved (Table 2) [4, 15].

Pathophysiology

The pathophysiological mechanisms are variable depending on the amount of fluid accumulated and the rapidity of the installation.

Progressive development of PE may cause pathophysiological disorders by:

- pulmonary compression, with pulmonary collapse, which leads to decreased ventilation and subsequent infusion, with right to left shunt hypoxemia;
- shift of the mediastinum to the same side with respiratory insufficiency, decreased venous return with cardiovascular disorders;
- metabolic disorders due to protein, liposoluble vitamins and fats loss, which can lead

Table 2 Etiologies of paraneoplastic PE (modified after Sahn SA) [4, 15]

Etiologies	Effects
Lymphatic obstruction (lymph nodes metastasis)	Accumulation of fluid by decreasing pleural absorption
Obstruction/rupture of lymphatic vessels	Chylotorax
Bronchial obstruction with atelectasis	Transudate
Bronchial obstruction with pneumonia	Exudate
Superior vena cava syndrome	Transudate (increased central venous pressure)
Pulmonary infarction	Exudate
Decompensated heart failure	Transudate (increased central venous pressure)
Constrictive pericarditis	Transudate (increased central venous pressure)
Ascites	Hepatic hydrothorax (through diaphragmatic pores) (Transudate)
Hypoalbuminemia (<1.5 g/dl)	Transudate
Paraneoplastic nephrotic syndrom	Transudate
Radiotherapy—in early phase (6 weeks–6 months)	Exudate (pleural inflammation)
Radiotherapy—in later phase	Transudate by superior vena cava syndrome (mediastinal fibrosis, constrictive pericarditis)
Chimiotherapy (cyclophosphamide)	Pleuropericardites

to advanced stages of severe malnutrition and death, and immunological alteration as a result of lymphocytes and antibodies loss, with an increased risk of severe infections (chylous effusions).

When PE develops rapidly, cardiopulmonary disorders suddenly occur with dyspnoea and tachypnoea, tachycardia, hypotension, and even shock.

Variants of Pleural Effusions Associated Cancers

In non-Hodgkin's lymphoma pleural effusion occurs more frequently in the large cell type than the small cell form [16]. Approximately 20% of PE associated with non-Hodgkin's lymphoma have the form of chylothorax [17]. In pleural cases associated with non-Hodgkin's lymphoma, pleural cytology of pleural effusion is positive in all cases. The presence of PE at the time of diagnosing non-Hodgkin's lymphoma does not seem to interfere with patients' response to treatment without affecting the remission of the disease or the outcomes [18].

Pleural effusions related to lymphomas. Hodgkin's lymphoma has mainly a pathogenic mechanism represented by the lymphatic obstruction due to the invasion of the mediastinal lymph nodes, while non-Hodgkin's lymphoma may cause directly pleural invasion [19].

The incidence of PE at the time of presentation is higher in patients with non-Hodgkin's lymphoma (6–50%) than patients with Hodgkin's lymphoma (7–21%) [20, 21].

Most patients with Hodgkin's lymphoma and PE present the type of lymphoma with nodular sclerosis [16]. Only 3% of PE associated with Hodgkin's lymphoma are chylothorax.

In non-Hodgkin's lymphoma PE occurs more frequently in the large cell type than the small cell form [16]. Approximately 20% of PE associated with non-Hodgkin's lymphoma develop chylothorax [22]. In PE associated with non-Hodgkin's lymphoma, pleural cytology (pleural effusion) is present in all cases. The presence of PE when diagnosing non-Hodgkin's lymphoma does not seem to interfere with patients' response to treatment, with disease remission and the surviving rate [18].

Pleural effusion associated with malignant mesothelioma develops from early stages, as a result of increased pleural capillary permeability due to direct invasion of pleura and by blocking lymphatic drainage of the pleural space. As the tumor grows, both visceral pleura and parietal pleura merge, resulting in the obliteration of the pleural cavity and the gradual reduction of the pleural fluid with its disappearance.

Pleural fluid is an exudate that contains in case of 1/3 cases of malignant mesothelioma, low levels of pH and glucose in pleural fluid (poor prognostic factors) [23]. The pleural fluid cytology shows the existence of a mixture of exfoliated mesothelial cells, some of which are normal and others with malignant features.

Usually, tumor marker levels from the pleural fluid are associated with malignancy, and are done in adults with breast, pulmonary, colon, prostate and ovary cancer [24]. Common tumor markers are carcinoembryonic antigen (CEA), cancer antigens 15-3 (CA 15-3), CA 72-4, CA 125, carbohydrate antigen 19-9 (CA 19-9), cyfra 21-1, cytokeratin fragment-21-1, stage-specific embryonic antigen-1, and nonspecific enolase [24].

Pleural effusion associated with lung cancer. Lung cancer is the most common cause of malignant PE in men. Approximately 15% of lung cancer patients has PE at the first time of assessment. During the disease, at least 50% of patients with lung cancer will develop PE [25].

Although all histological types of pulmonary cancers can develop PE, adenocarcinoma is most commonly involved in malignant pleural disorders and in the occurrence of neoplastic PE, probably due to its predominantly peripheral location. The incidence of neoplastic PE is lower in patients with small cell lung cancer (~15%) [26].

The association of paraneoplastic PE (type II) does not rule out the surgery intervention in lung cancer of stage I, II or IIIA. In case of true malignant PE (type I), positive cytology and negative pleural biopsy (absence of pleural metastasis) may classify lung cancer in stage IIIB (malignant pleural effusion T4). In the presence of pleural metastases, lung cancer is in stage IV (M1 pleura). Pleural metastases of lung cancer are most commonly found on both pleural (visceral and parietal) surfaces, rarely only on the visceral face and never only on the parietal pleura. Visceral pleural metastases occur either contiguously from the pulmonary tumor invading the visceral pleura, or by invasion of the pulmonary arteries (neoplastic embolization). Once they reach the surface of the visceral pleura, the malignant cells migrate to the surface of the parietal pleura along the adherence zones or exfoliation. Malignant PE in lung cancer may be ipsilateral or bilateral (bilateral metastases) and never just contralateral, or it is associated with pericarditis.

Relatively recent studies show the importance of DNA analysis in malignant cells present in pleural fluid to determine the existence of the epidermal growth factor receptor (EGFR) mutation. It seems that the presence of this genetic mutation is a predictive factor for the response of non-small cell lung cancer to EGFR (EGFR tyrosine kinase inhibitors—gefitinib) inhibitors [27, 28].

Breast cancer associated pleural effusion may be ipsilateral or with no specific localization. It is due to lymphatic invasion of the thoracic wall with ipsilateral PE and haematological metastasis with liver damage and bilateral or unilateral (ipsilateral or controllateral) pleural effusion. In breast cancer, the mean time span between primary tumor development and pleural effusion is between 2 and 5 years [29, 30] but this range can be up to 20 years [31].

Clinical Picture

Small PE are asymptomatic. Large PE causes dyspnea, cough, chest discomfort. Physical examination include dullness on percussion (upper limit with the shape of the Damoiseau curve) and diminution of breath sounds and reduced tactile and vocal fremitus. Pain occurs when the malign process affects the parietal pleura or the chest wall. Pain can be located strictly at the level of the invasion area or may

radiate in the shoulder or epigastrium (invasion of the diaphragmatic pleura). In PE associated with advanced lung cancer, palpation of lymphadenopathy or the presence of neoplastic cachexia can be noted.

Imaging Investigations

The CXR supports the clinical diagnosis of PE through several characteristic elements. **Small** PE (200-300 ml) produce opacification of the lateral costophrenic sinus, being detectable on the anterior X-ray [32]. The **moderate** PE (over 500 ml) and **large** PE (over 1500 ml) generates an intense, homogeneous radiological opacity with the upper concave upper limit (the meniscus sign) corresponding to the Damoiseau curve established at the percutaneous examination (Fig. 1) [32].

In large PE (over 1500 ml), the radiological absence of mediastinal shift supports the diagnosis of cancer (Fig. 2). Thus, we can find ourselves in front of a lung cancer that has produced atelectasia by obstruction of a major bronchus or which has fixed the mediastinum by lymphatic nodes metastasis ("frozen mediastin"). Opacification of the hemithorax may also be due to pleural tumors in mesothelioma (reduced pleural effusion) or extensive pulmonary tumor infiltration that mimics the radiological appearance of a massive PE [33].

CT examination plays a very important role in investigating malignant PE (Figs. 3 and 4). This can detect the presence of the primary tumor and even pleural metastases can be visualized (requires thin sections at 2 mm intervals).

In PE of unspecified etiology, CT exam can helps with useful information regarding the malign or benign findings of PE. Consequently, the following CT findings are considered suggestive of malignancy: (1) nodular pleural appearance, (2) rind or circumferential thickened pleural image, (3) lesional damage of the mediastinal pleura, (4) pleural thickening greater than 1 cm [34].

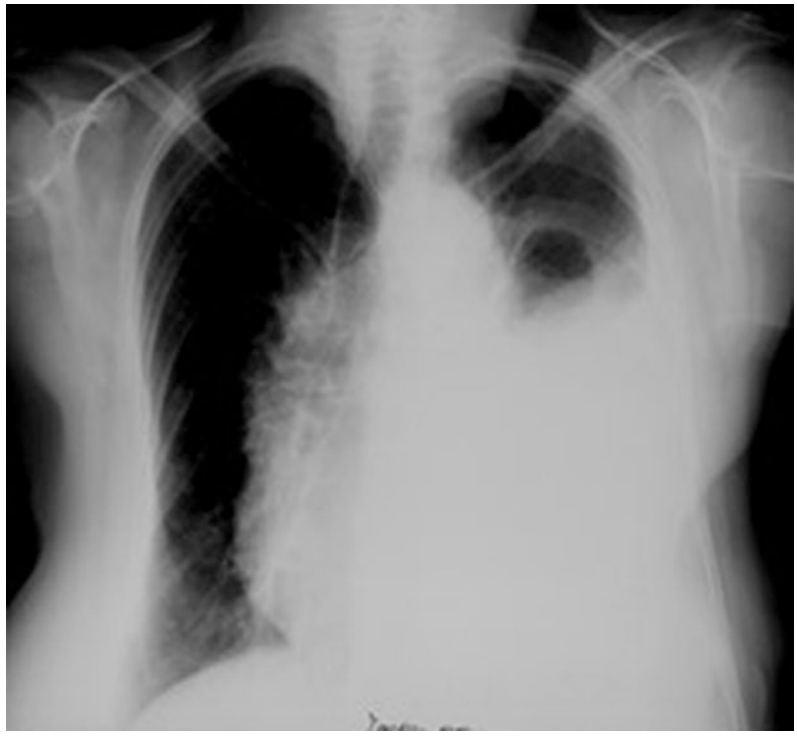

Fig. 1 High, homogeneous radiographic opacity with upper limit concave upwards (meniscus sign)

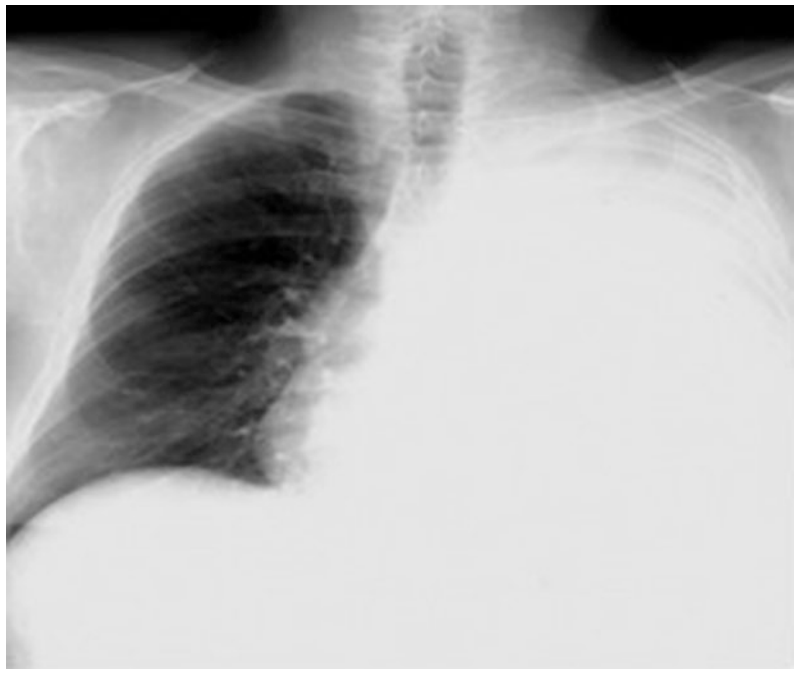

Fig. 2 Large PE (over 1500 ml), with the radiological absence of mediastinal shift movement ("frozen mediastin")

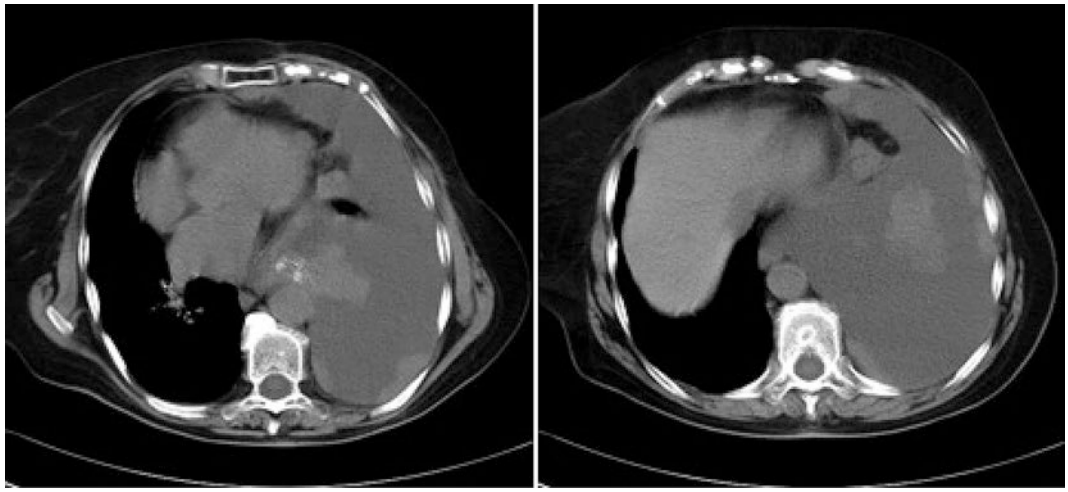

Fig. 3 Neoplastic pleural effusion with CT visualization of pleural metastases

In some cases with malignant PE, other CT signs have also been reported such presence of neoplastic pericarditis, thickened pericardium (pericardial tumor infiltration), mediastinal lymphadenopaty (lymphatic nodes metastases), chest wall lesions by parietal invasion produced by the pleural malignant process, pulmonary tumor-like, nodular and infiltrative lesions (presence of primary tumor or disseminated secondary lesions).

CT exam can help along with the ultrasound examination in the detection and treatment of

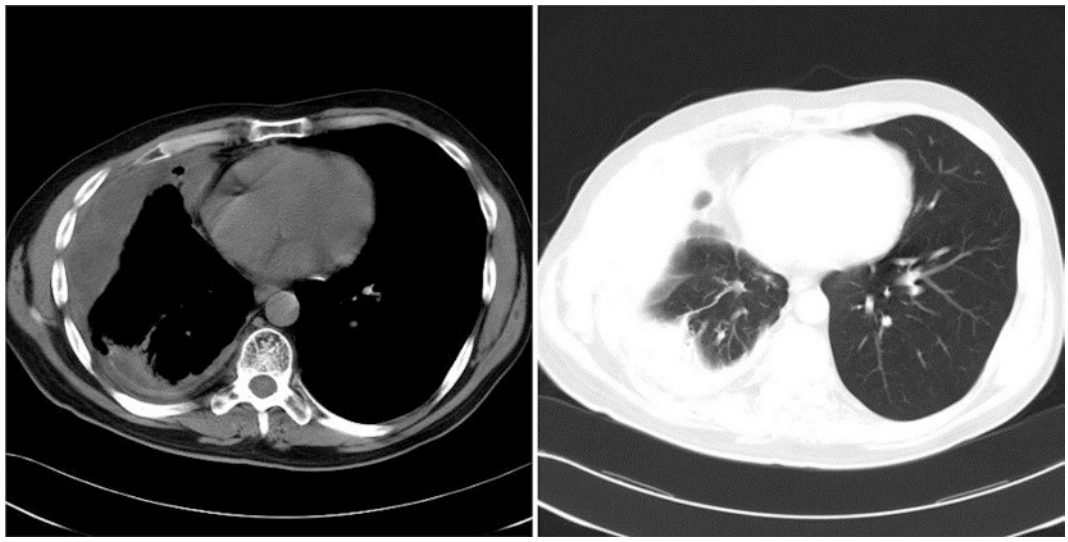

Fig. 4 CT exam of neoplastic PE in a diffuse pleural mesothelioma

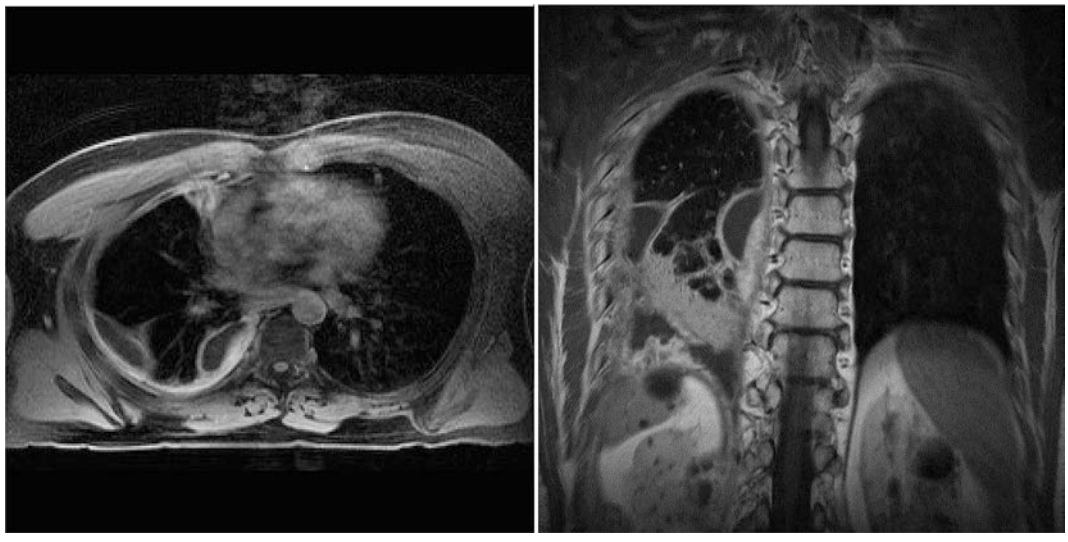

Fig. 5 MRI exam of neoplastic pleural effusion in a diffuse pleural mesothelioma

malignant PE by identifying the puncture site or surgical site.

MRI examination may be useful in the investigation of pleural mesothelioma by appreciating the invasion of the thoracic wall, diaphragm, mediastinum and pericardium (Fig. 5).

In recent years, modern medicine has benefited from the emergence and development of a new technology for the investigation of neoplasms, which belongs to nuclear medicine and which is based on the principle of increasing the metabolism of glucose in the tumor cells. Known as *PET (Positron Emission Tomography)*, radiolabeled F-18 analogue of 2-deoxyglucose (18-FDG) is used as the radiopharmaceutical substrate. This method, applied alone or in combination with CT, can be successfully used in the differentiation of

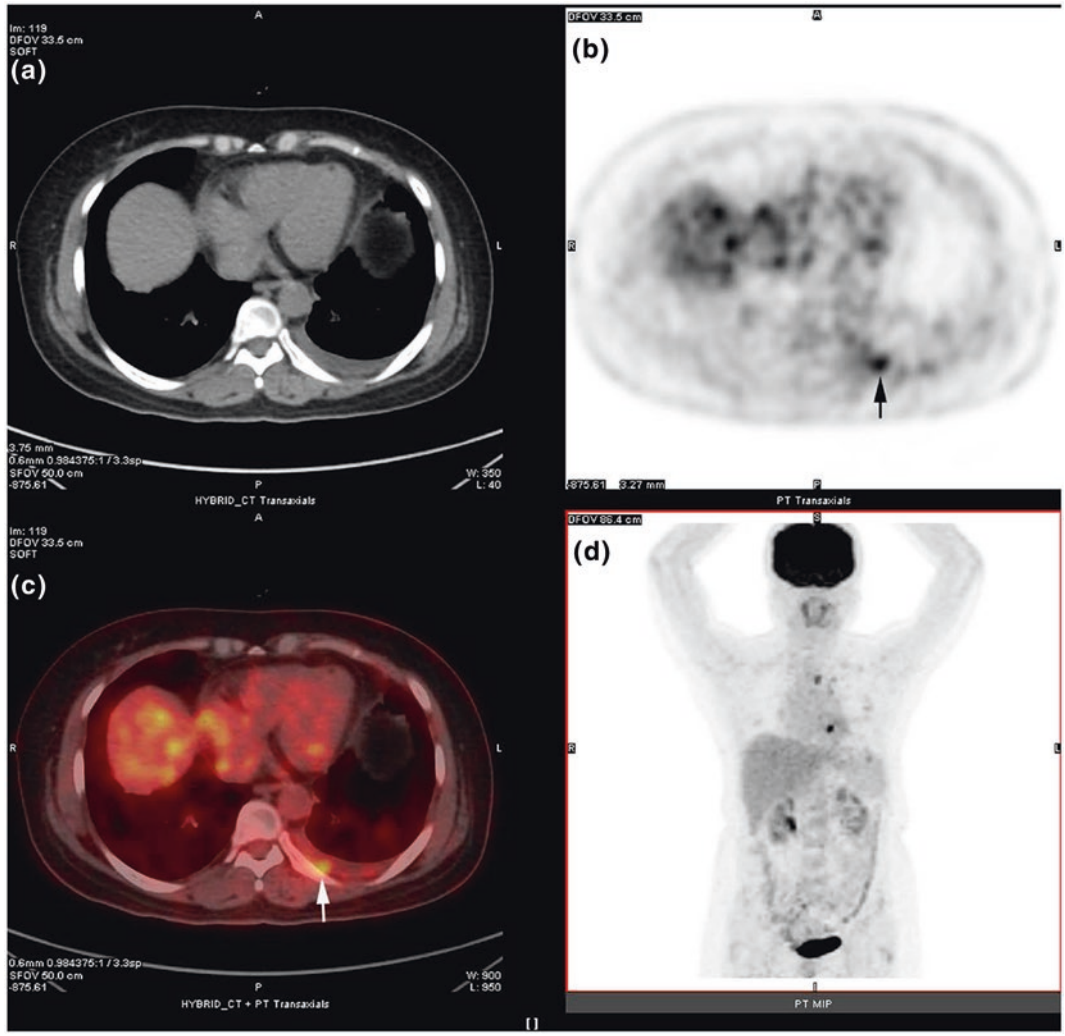

Fig. 6 ^{18}F-FDG PET/CT integrated imaging of 54-year old woman with left lung cancer and malignant pleural effusion. Axial CT **a** shows effusion in left pleural cavity, and axial ^{18}F-FDG PET (**b**, arrow) and axial fused ^{18}F-FDG PET/CT (**c,** arrow) display nodular ^{18}F-FDG uptake (SUVmax of 3.0) in left-posterior pleural region. Pathology from thoracentesis confirmed malignant pleural effusion caused by metastatic adenocarcinoma. From [37]. This is an **open access article** distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited

malignant and benign PE in the assessment of primary and metastatic pleural tumors (Figs. 6, 7 and 8) and in the evaluation of their response to treatment [35–37]. To sum up, ^{18}F-FDG PET/CT integrated imaging represents a better consistent is a more reliable technique in the separating of benign PE from malignant PE than ^{18}F-FDG PET imaging and CT imaging alone [37]. Although it provides very important diagnostic elements, this technique can not substitute for the histopathological verdict due to the possible false results it can issue. Consequently, tumors such as epithelial malignant mesothelioma, which have a reduced metabolic activity, are difficult to differentiate from benign tumors.

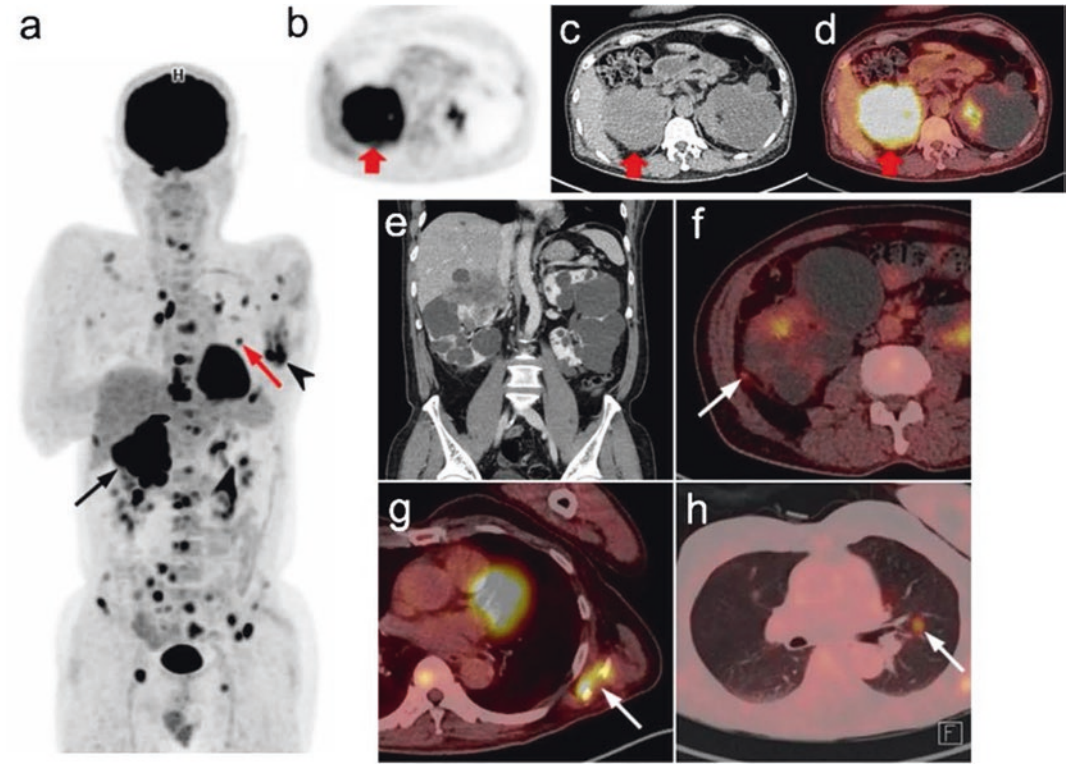

Fig. 7 Maximum intensity projection (MIP) image of whole-body 18F-FDG PET (**a**) revealed a focal intensely increased activity at the right suprarenal region (arrow) with a maximum standardized uptake value (SUVmax) of 15.6 and also multiple increased activity foci at numerous bones, including the left scapula (arrowhead), and left lung (red arrow). On axial image (**b**, PET; **c**, CT; **d**, fusion) the increased activity (red arrows) corresponded to the huge mass ($8.8 \times 7.1 \times 6.8$ cm) on CT with ill-defined lobulating margin, whose epicenter was located at the superior aspect of the right kidney with inner heterogeneous low attenuation that suggested a necrosis. The mass encased the IVC and extended to the liver. Coronal CT image (**e**) demonstrated multiple simple cysts at both kidneys and liver, compatible with known PCKD. Metastatic lesions at a perirenal lymph node (**f**), bones (**g**) and left lung (**h**) were also depicted. From [36] with **permission**

Characteristics of the Pleural Fluid

Neoplastic PE may be serous, sero-sanguinous or haemorrhagic frank. The hemorrhagic appearance of the pleural fluid suggests the existence of pleural neoplastic invasion, while the serous character may be caused by tumor lymphatic blockage or atelectasis secondary to endobronchial obstruction. In some cases retrograde lymphatic pressure, generated by neoplastic lymphatic obstruction, can cause breakage of accessory lymphatic channels or even the thoracic duct, with the appearance of the chylothorax.

Light et al. sustain that in the presence of erythrocytes greater than 100.000/μL in the pleural fluid, in the absence of any trauma (spontaneous hemothorax), cancer is most likely diagnosed [38].

The most common nucleated cells observed in malignant PE are lymphocytes, macrophages and mesothelial cells (½ cases of lymphocytes are >50%) [39]. In rare situations (intense pleural inflammation), polymorphonuclear cells may predominate. In 7.8% of cases studied by Rubins, eosinophils prevailed [40].

As already mentioned, PE associated with cancers can be exudate or transudate. Malignant

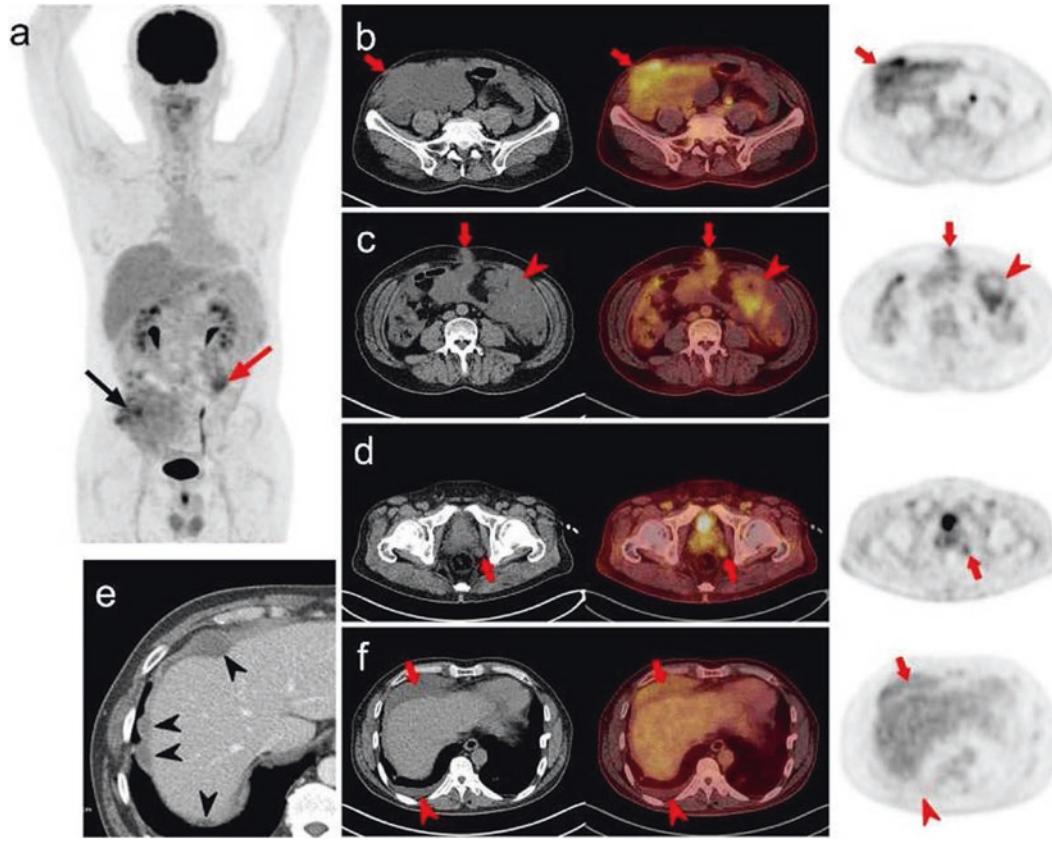

Fig. 8 Maximum intensity projection (MIP) image of whole-body 18F-FDG PET (**a**) demonstrated two areas of increased uptake in the RLQ (black arrow) and left para-umbilical region (red arrow) which correspond to an irregular peritoneal mass beneath to the appendectomy scar (**b**) and caked omentum in the left sided abdomen (**c**, arrowhead) in the axial PET/CT images; SUVmax 5.5 and 3.4, respectively. An umbilical nodule extended from peritoneal mass in the mid abdomen also showed increased ^{18}F-FDG uptake (**c**, arrow). A hypermetabolic mass at the rectal shelf (**d**) was depicted. Loculated ascites with scalloping to the liver surface was best visualized in contrast-enhanced CT image (**e**), which showed minimal increased uptake (**f**, arrow), consistent with malignant ascites. ***Hypometabolic right pleural effusion*** without pleural lesion was considered benign causes (**f,** arrowhead). From [36] with **permission**

pleural effusions (type I) are exudates with a protein concentration of >3 g/dl and LDH > 200U/L. The existence of pleural transudate associated with cancers suggests their paraneoplastic nature (type II malignant PE). There are also PE that meets the transudate protein criteria but not LDH. Many of these PE are neoplastic [2].

After Sahn and Good, approximately one-third of neoplastic PE have a low pH (<7.30) and a low glucose (<60 mg/dl) (severely affecting the pleura reduces both the glucose influx into the cavity pleural effusion and efflux of glucose degradation products in the pleural area, and local acidity increase) [1, 19]. In these cases, the authors note low survival, greater probability of diagnosis by cytology and pleural biopsy, and poor response to intrapleural sclerosing agents.

The most widely used **tumor marker** in pleural fluid is the CEA. It has, according to some authors, an increased specificity for the neoplastic process (at values >5 ng/ml), but in same time exhibits a relative lack of sensitivity [41, 42].

Fluid Cytology Diagnosis

The cytological examination of the pleural fluid might identify the malignant cells in about 50% of cases [24]. Based on Lights criteria, the malignant PE is usually an exudate [24].

Pleural cytology has an average sensitivity of 60%, with limits between 43 and 96%, after Moghissi [5], laboratory-dependent and pleural type (more positive results in large haemorrhagic PE). However, the specificity of cytology is close to 100%.

By comparison, the sensitivity of the pleural biopsy puncture is 44% and the thoracoscopic pleural biopsy reaches 95% [33].

The sensitivity of cytology can be improved by applying new detection techniques using monoclonal antibodies, cytogenetic techniques, molecular biology (RT-PCR for the detection of neoplastic epithelial cells, identification of specific molecular alterations such as k-ras mutation, telomerase activity, etc.).

Histopathological Diagnosis

Pleural tissue can be obtained through mini-invasive (closed) techniques such as percutaneous pleural needle biopsy and thoracoscopic pleural biopsy or chest opening methods (pleural biopsy through thoracotomy).

The percutaneous pleural needle biopsy (blind pleural biopsy) is a complementary technique to the cytology exam, with a lower diagnostic sensitivity than it (44 vs. 60%). This is explained by the fact that approximately 50% of patients with malignant PE have only visceral pleura affected by neoplastic lesions [43] and, when present, the lesional involvement of the parietal pleura in metastatic PE is uneven. Taken together they achieve a combined sensitivity of 74% (vs. 95% for thoracoscopic biopsy) [44].

Generally, the sensitivity of the method is largely influenced by the type of used instrument, the size of harvested material and the operator experience. As a blind maneuver, an important role in the successful diagnosis is the biopsy site. Using the information provided by the thoracoscopy, the sensitivity of the method can be improved by taking biopsy material from a site as close as possible to the diaphragm and backbone (an elective site for spreading pleural metastases). Also, the accuracy of the method can be increased by performing the biopsy under CT control from thickened parietal pleural areas (CT-guided percutaneous pleural biopsy).

Thoracoscopic pleural biopsy. The thoracoscopic examination of the pleural cavity can be performed either under local anesthesia (especially in severe malnutrition) or under general anesthesia. It allows to perform multiple targeted biopsies from lesions of the pleura, lung and mediastinum (Fig. 9).

Cytological examination of pleural fluid by percutaneous pleural needle biopsy, is indicated in PE without etiologic diagnosis, in patients with recurrent PE or with neoplastic history, or when malignant etiology is suspected. Some authors reported the existence of four predictive features for the neoplastic aetiology of PE such as (1) more than one month of respiratory symptoms, (2) absence of fever, (3) presence of haemorrhagic pleural fluid, and (4) radiological evidence of suggestive signs of cancer (pleural or lung masses, pulmonary atelectasis, increased mediastinal opacity or hilum opacity cause by lymphadenopathy) [45].

This diagnostic method is superior to previous techniques, reaching a sensitivity of 80 to 100% [46]. However, there are studies attempting to increase the diagnostic sensitivity of this method to 100% by combining thoracoscopy with thoracoscopic fluorescence diagnosis (TFD) [47]. These authors use 5-aminolevulinic acid (ALA) as a natural precursor to the hem synthesis as photodynamic agent. Administration of ALA either systemic (intravenous) or topical (intrapleural lavage with 3% ALA) results in the accumulation in the tumor cells of a photosensitive metabolite—protoporphyrin IX (Pp IX). For maximum diagnostic sensitivity, thoracoscopy is performed 6 hours after ALA administration. The use of red light at

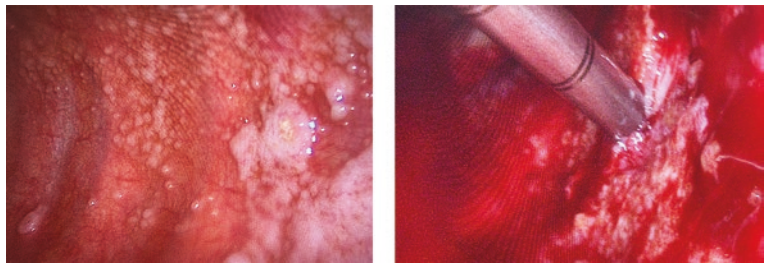

Fig. 9 Thoracoscopic pleural biopsies targeted to parietal pleura lesions

thoracoscopy reveals Pp IX fluorescence even in invisible tumor sites by conventional white light.

Pleural thoracotomy biopsy (open)
It is reserved only for up to 20% of PE left undiagnosed by the previous methods. Published data showed that about 50% of these PE have been found to be neoplastic following the biopsy performed by thoracotomy [48]. Toracotomy is also indicated in undiagnosed PE associated with pulmonary or pleural lesions, being in the same time a therapeutic option.

To sum up, in Fig. 10, we propose an algorithm for the evaluation of a pleural effusion.

Treatment of Malignant Pleural Effusions

The treatment of PE associated with cancers is based on the precise knowledge of the presence or absence of pleural metastases. In the absence of these, we are facing a paraneoplastic PE, the treatment of which is a specific one addressed to the primary tumor. In these situations, therapeutic control of primary cancer leads to the eradication of PE. In the presence of pleural metastases, the fluid may accumulate in large amounts, producing respiratory failure phenomena. In these cases, a non-specific, palliative treatment should be instituted with the sole purpose of treating PE, to improve the patient's life comfort.

Specific treatment
In lung cancer associated PE, in patients with good general health, in the absence of neoplastic cells in the pleural fluid or in fragments collected by pleural biopsy puncture, the therapeutic sequence includes obligatory thoracoscopy performed under general anesthesia. In the absence of pleural metastases, under the same anesthesia, the thoracotomy is performed with lung tumor resection. In the presence of pleural metastases, thoracoscopic pleurodesis, as a non-specific treatment means, remains to control the accumulation of pleural fluid.

In PE of pleural mesothelioma with I Butchart stage, one can also speak of a specific surgical treatment associated with pre- and post-operative radiotherapy. Complete removal of the primary (pleural) tumor can be achieved by choosing one of the two surgical procedures: (1) pleuropneumonectomy in a closed vessel, or (2) pleurectomy with decortication.

In other situations, specific treatment may include chemotherapy (lymphoma-associated PE, breast cancer or lung cancer), hormone therapy (breast cancer) or radiotherapy on the neoplastic mediastinal lymph nodes (lymphadenopathy PE from small cell lung cancer or from lymphomas). With respect to the oncological treatment of patients with malignant PE secondary to bronchial-pulmonary cancer, there are authors who cite favorable results obtained by administering cisplatin, ifosfamide and irinotecan to 34 patients with NSCLC and neoplastic

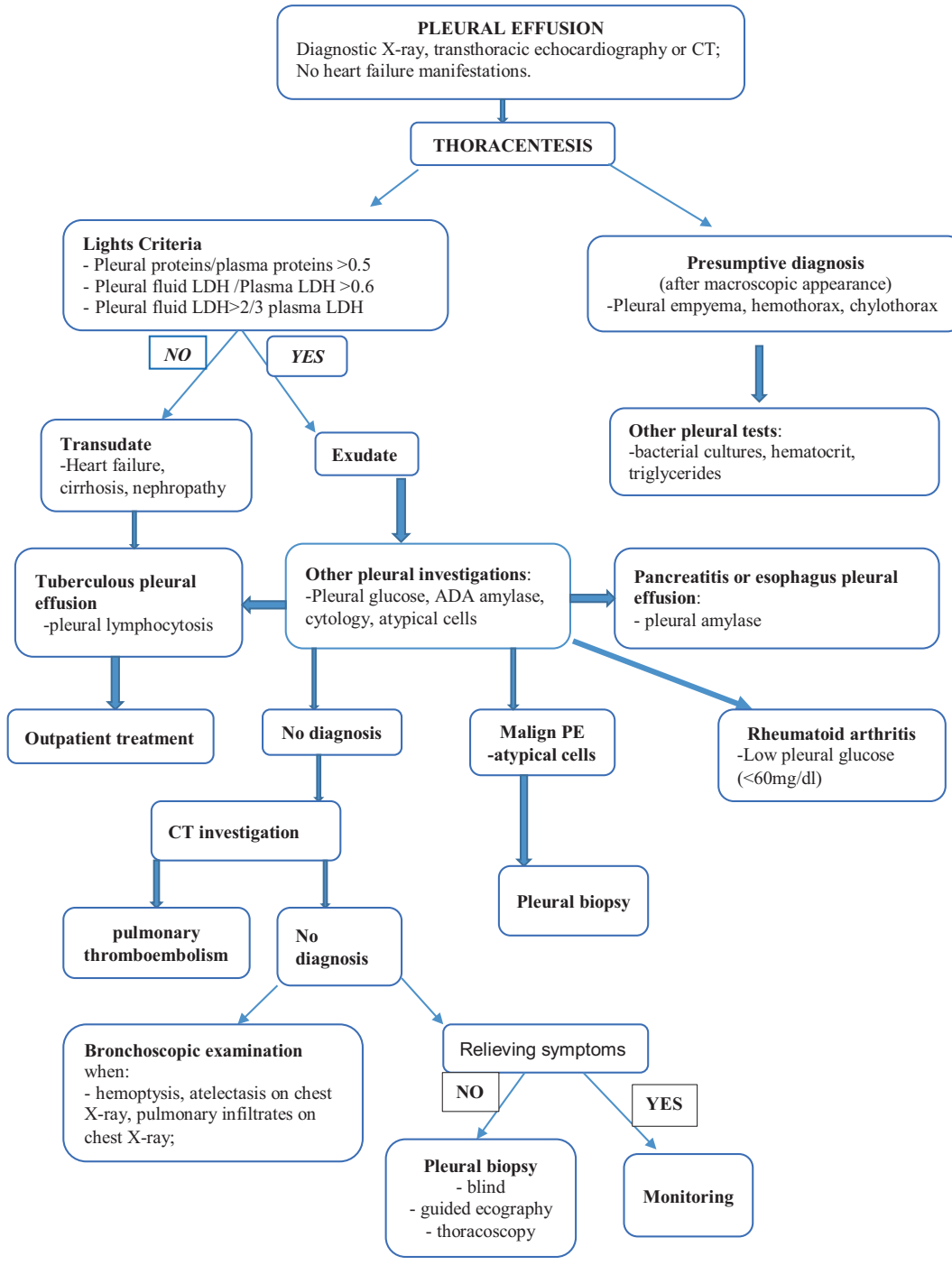

Fig. 10 Proposal algorithm for evaluation of a pleural effusion

pleural effusion, with complete disappearance of pleural effusion in 13 patients (38%), partial resolution in 7 cases (21%) and mean survival time of 362 days [6]. The same author underlines the possibility that this regimen may be useful in the treatment of patients with lung adenocarcinoma, who are predicting an increase in survival [6]. Other recent studies show increased survival in patients with neoplastic pleural effusions in NSCLC, in addition to treatment with anti-VEGF antibodies (bevacizumab) in addition to the standard first-line chemotherapy [49]. It is important, however, that anti-VEGF treatment should not be used in patients using different chemical or mechanical processes of PE because angiogenesis plays a potent role in achieving effective pleurodesis [50].

Non-specific treatment

In true malignant PE (type I), the patient is not a candidate for curative surgical treatment, and the clinician must choose a non-specific, palliative treatment method. In choosing the palliative treatment method we must weigh a number of factors such as age, general state, symptom severity, associated pathologies, and last but not least, we have to consider the average life expectancy.

Thus, asymptomatic PE, quantitatively reduced, can be observed without taking any therapeutic measures.

In dyspnea, elderly or severely associated severely ill patients, it is more prudent to choose less invasive palliative methods such as repeated thoracentesis (without hospitalization) or drainage of the pleural cavity through minimal pleuretomy with or without pleurodesis on the drain tube (requires a short hospital stay). In this group of patients, a thoracoscopy with local anesthesia may also be considered when there is no diagnosis of pleural neoplastic disease.

In symptomatic patients who have a biologically acceptable status without severely associated severe pain, it is preferable to perform a thoracoscopic surgery under general anesthesia with the intraoperative assessment of pulmonary expansion depending on whether or not a method of pleurodesis is associated (intraoperative insufflation of talc).

As a spare palliative method, thoracotomy with pleurectomy should be considered due to the increased morbidity and mortality involved. This therapeutic remedy can only be attempted in patients with good general health who have an expected survival of at least 6 months. These are the patients who have the lung trapped in a visceral pachypleuritis, or whose pleural effusion has relapsed after pleurodesis.

Pleurodesis

It aims to stop the accumulation of pleural fluid. This is accomplished by the obliteration of the pleural cavity by creating fibrous adhesions between visceral and parietal pleura.

Pleurodesis should be considered in symptomatic (dyspneic) patients with malignant PE (except for malignant chylothorax) refractory to chemotherapy, which has been shown to significantly relieve respiratory distress after evacuation thoracentesis.

Performing pleurodesis should be preceded by a careful paraclinical assessment of the patient. The presence of mediastinal shift on the part of PE requires compulsory bronchoscopic examination that should be performed with the assessment of the existence of a possible bronchial obstruction, in which pleurodesis is contraindicated.

The introduction of the method was necessary because most of the neoplastic PE are refractory to chemo and radiotherapy.

Intraoperative pleurodesis (thoracoscopic or by thoracotomy) is by injecting powders with sclerosing effect (e.g. talc). Postoperative pleurodesis consists of the intrapleural instillation of fibrous solutions on the drainage tube introduced by minimal or thoracoscopic pleurotomy.

An important principle to be observed for making an efficient pleurodesis is to obtain a fully drained pleural cavity and a complete pulmonary expansion before using sclerosing agents. This allows adhesion between the two

pleural sheets in contact. According to their effects, substances used for pleurodesis can be divided into two main categories: cytotoxic agents (controlling PE by reducing tumor volume) and sclerosing agents (proinflammatory, fibrinogenic). Overall, agents for chemical pleurodesis comprise bleomycin, tetracycline/doxycycline, Corynebacterium parvum extract, silver nitrate, iodopovidone, quinacrine, interferons, and interleukin-2 [24]. Regarding the use of talc, based the comparisons involving effectiveness, morbidity, and convenience, we recommend the thoracoscopic insufflations of talc as a fine powder with pleural drainage as the procedure of choice [51].

The cytostatic agents

Most of them also have sclerosing effect. Thus, radioactive colloids, bleomycin, doxorubicin and mustard nitrogen combine both effects, predominantly their sclerosing character. The exception is cisplatin, thiotepa and 5-fluorouracil, the predominant effect of which is tumor reduction. Most cytotoxic agents have been abandoned either due to inefficiency or increased toxicity (pain, fever, nausea, vomiting, etc.).

A special mention deserves bleomycin, which is currently the most used intrapleural cytostatic, primarily due to its sclerosing effect. For instance, Ruckdeschel and Rubins conducted a prospective randomized trial to compare pleurodesis with tetracycline 1 g and 60 U of bleomycin [40]. The study showed the superiority of bleomycin, both as a sclerosing effect and lower pleural pain. Although generally well tolerated, bleomycin may occasionally have nephrotoxic effect in patients with pre-existing renal insufficiency.

Cisplatin was most commonly used intraperitoneally for the treatment of ovarian cancer with peritoneal metastases. Its predominant effect is neoplastic regression, having a tumor penetration power of about 5 mm by intrathoracic administration. According to Markman, the use of cisplatin is not effective in the presence of bulky pleural/peritoneal tumors [52]. A study on the intravenous administration of cisplatin to neoplastic PE [53] shows an average efficacy and increased systemic absorption, which is why it is not routinely used.

Radioactive colloids such as zinc (63Zn), gold (198Au) and chromate (Cr32PO4) phosphate have been associated with low toxicity but with modest and cost-effective efficiency, so they are not routinely used in the treatment of neoplastic PE [54].

Sclerosing agents

The tetracycline pleurodesis was introduced in 1972. It has the advantage of being cheap, relatively nontoxic and quite effective in the treatment of malignant PE. Its major adverse effect is pleural pain, sometimes difficult to control, even through intrapleural administration of xylene, often requiring peridural analgesia. With the cessation of production of tetracycline hydrochloride, other substances in the tetracycline group have been shown to be effective in treating neoplastic pleural effusion: minocycline 300 mg and doxycycline 500 mg.

Talc pleurodesis was first used by Bethune in 1935. Because it is insoluble, talc is more commonly administered as a powder either by insufflation during thoracoscopy (Fig. 11) or, more rarely, by thoracotomy. In patients unable to undergo surgery, it is preferable to administer a suspension of talc on the drain tube after pleurotomy or after thoracoscopy with local anesthesia.

There are studies showing similar efficacy (almost 90%) in the treatment of neoplastic PE both by intraoperative powder (insufflation of talc powder) and by insufflation of talc suspension on the drain tube [51]. Based on our cases, we have noted the superiority of the intraoperative powder, probably by a more uniform distribution of the talc particles throughout the pleural area [51]. On the basis of comparisons involving effectiveness, morbidity, and convenience, we recommend the thoracoscopic insufflations of talc as a fine powder with pleural drainage as the procedure of choice [51]. Respecting the principles of pleurodesis, use of talc requires the

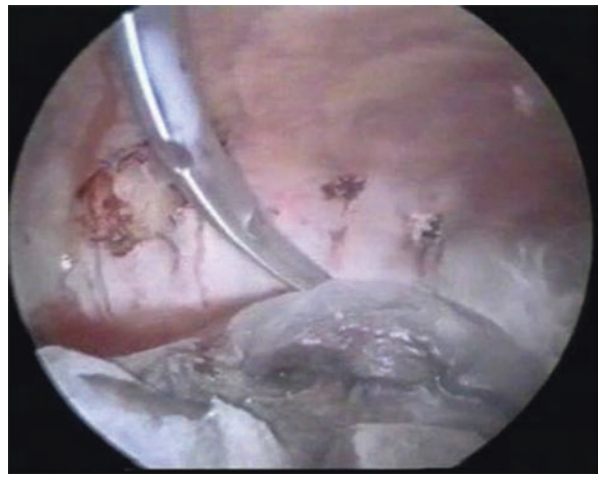

Fig. 11 Intraoperative aspect of the pleural cavity after talc insuflation

presence of a complete pulmonary expansion and the complete drainage of the pleural fluid. This avoids the increased risk of infection with the residual cavities powdered with talc.

Predictors of the ineffectiveness of talc or tetracycline chemical pleurodesis (in approximately 10% of patients) were pleural pH below 7.2 and low glucose concentration below 60 mg/dL [55]. The success of pleurodesis is also influenced by the type of malignant pleural effusion generating primary neoplasia. Hence, Bielsa et al. have shown lower efficacy of talc or doxycycline chemical pleurodesis in patients with lung cancer and pleural mesothelioma compared to patients with breast cancer secondary pleurisy and other primary tumors [56]. In order to achieve an effective pleurodesis, simultaneous treatment with anti-inflammatory drugs (corticoids or NSAIDs) should be avoided.

Making chemical pleurodesis with sclerosing agents does not improve survival but has the advantage of improving the quality of life of patients by controlling respiratory phenomena.

The talc prepared for medical use should be free from asbestos, the particle size should be <50 μm and especially must be sterile. Sterilization can be done with dry heat, gamma rays or ethylene oxide [57]. The talc remains sterile for at least 1 year. The dosage used for talc may be between 2 and 5 g.

The side effects that accompany pleurodesis with talc may be fever and pleural pain (much less severe than tetracycline). Rarely, these patients may develop adult respiratory distress syndrome (SDRA) (culminating with their death) [58], which is sometimes correlated with the use of larger amounts of talc and reduced talc particle size. Therefore, the use of talc preparations containing very small particles (<10 μm) is not recommended. Another complication related to the intrapleural use of talc is pulmonary thromboembolism (even the death of patients). This complication, cited by some authors, may be associated with an increase in serum IL-8 level with known procoagulant effect in patients with pleural talc [59].

If is of note, intrapleural talc administration generates pleural chronic inflammation that causes increased F-18 fluorodeoxiglucose uptake in the PET-CT assay [60].

Drain tube pleurodesis technique (adapted after Sahn) [33]:

1. Placing the drainage tube on the medial axillary line and oriented towards the diaphragm;
2. Gradual evacuation of the pleural fluid and passive drainage under the protection of 100 mg i.v. hydrocortisone hemisuccinate (to avoid rebound pulmonary edema);

3. Radiological control of the position of the drain tube;
4. Connect drain tube to active suction (−20 cm H_2O) (after 24 hours);
5. Radiological checking of complete pulmonary expansion and absence of pleural fluid;
6. General analgesia (midazolam or narcotic iv) or local (xylin on the drainage tube <150 mg or 3 mg/kg body) or loco-regional (peridural analgesia);
7. Sclerosing agent instillation and tube clamping 1 hour:
   a. 300 mg minocycline in 50 ml physiological saline or
   b. 500 mg doxycycline in 50 ml physiological saline or
   c. 2–5 grams of talc in 100 ml physiological saline;
8. Change of decubitus of patients instilled with talc suspension (tetracycline instillation does not require maneuver, the sclerosing agent being distributed uniformly in the pleural cavity);
9. Connect the tube to active suction (−20 cm H_2O);
10. Extraction of drain tube, when drainage reaches less than 100 ml/24 hours.

Instillation of cytostatic agents requires longer contact with metastatic pleura (approximately 4 hours for cisplatin) [53].

Other sclerosing agents

Silver nitrate was the first chemical used to produce pleurodesis. In the 1980s, silver nitrate was replaced by tetracycline due to adverse reactions from the use of high concentrations of this substance. There are studies in debate to re-use silver nitrate (20 ml 5% solution) instilled on the pleural drain tube. These authors demonstrated superior efficacy in obtaining pleurodesis for silver nitrate (96%) compared to talc (84%) [61].

Iodopovidone (betadine) is also a very potent agent of pleurodesis. The recommended dose of various authors is 100 ml of 2% betadine solution [62] or 50 ml of 2% betahistine solution [63] administered either at the end of the thoracoscopic surgery or on the pleural drainage tube. In these studies, the efficacy of betadine in preventing the re-accumulation of malignant pleural fluid was similar to talc, while adverse reactions were lower than that. As side effects of betadine used at recommended doses, intense pleuritic pain and systemic hypotension may occur in some patients [62]. There were no deaths due to the use of betadine. Other authors, using 200–500 ml of 10% betadine (more than 25 times recommended doses) reported 3 cases of loss of vision [64]. Recent studies place betadine as an effective alternative to tetracyclines and talc in the production of pleurodesis in patients with neoplastic PE [6].

There are authors who have successfully used intrapleural instilled immunomodulators in the treatment of lung cancer-associated malignant PE (NSCLC) [65]. They demonstrated the efficacy of intravenous administration of the superantigen of Staphylococcus aureus (SSAg) (a strong immunostimulator of T lymphocyte activity), not only achieving pleural effusion control but also increasing patient survival.

Based on the observation of the role of cytokines in the induction of fibrosis, animal studies were performed using transplanted growth factor-β (TGF-β) instillation which is a cytokine with a strong fibrinogenic activity [66]. These investigations have shown that incubation of human pleural mesothelial cells together with TGF-β determines the phenotypic transformation of these cells into fibroblasts. Preliminary results have shown that intrapleural injection of small amounts of TGF-β generates better pleurodesis than intrapleural inhalation of talc or doxycycline by fibrin formation effect without causing pleural lesions as other pleurodesis agents. In this case, TGF-β could be in future an ideal agent for pleurodesis, which will have to be demonstrated by clinical trials in patients with neoplastic PE.

Due to the risk of death by acute respiratory failure (ARDS, TEP) that intrapleural administration of talc presents, and because the effectiveness of talc chemical pleurodesis is not significantly higher than for other substances, it is useful to look for alternative pleurodesis methods in neoplastic PE. Light [66] identified

the three best alternatives to talc pleurodesis: (1) pleural mechanical abrasion, (2) instillation of 100 ml of 2% betadine (iodopovidone) solution and (3) intrapleural instillation of 1 gram of bovine collagen powder. Among these, the author considers pleural mechanical abrasion to be the best pleurodesis that can be used intraoperatively (by thoracoscopic surgery), both due to the lack of reactions and complications, and due to the findings of studies showing the existence of a longer hospitalization duration for patients undergoing intraoperative talc insufflation.

Treatment of Neoplastic Pleural Effusions with Trapped Lung

Patients who are found to have no pulmonary expansion after pleural fluid evacuation are not candidates for sclerosing agent therapy and are unlikely to benefit from intrapleural instillation of cytotoxic agents (they often have bulky pleural metastases).

In these patients, where we can not practically to stop the production of fluid, the drainage of the pleural fluid is first single purpose of ameliorating the respiratory symptomatology.

One method of intermittent drainage of pleural fluid is to mount a Denver pleuroperitoneal shunt with a one-way valve. Patient cooperation or family support is required; the pump chamber mounted in a subcutaneous pocket over the anterolateral lateral edge of the ribs requires approximately 25 compressions every 4 hours (to obtain a one-way pleural peritoneal drainage).

An alternative to intermittent drainage of the pleural fluid is the fitting of a permanent pleural drainage catheter (á demeure) (e.g., Pleurx). It can be used by the patient and family at home to evacuate the pleural fluid when the patient becomes symptomatic.

A special category consists of patients with good biological status, which may be subjected to a pleurectomy/decortication by thoracotomy, even if it has a significant morbidity and mortality [67].

Prognosis

Malignant PE have poor prognosis. Patients with lung, stomach or ovarian cancer generally survive only a few months after the diagnosis of neoplastic PE. In contrast, breast cancer patients can survive for several months or years, depending on the response to chemotherapy. Patients with neoplastic PE within lymphomas tend to have an intermediate survival between breast cancer and other carcinomas.

After Sahn, patients with low pH (<7,30) and low glycose (<60 mg/dL) neoplastic patients survive for only a few months, while patients with normal values of these parameters can live approximately 1 year [33]. It can be said that the biochemical examination of the pleural fluid can provide useful information in choosing the appropriate treatment plan in the neoplastic PE.

In lung cancer, PE is the most common neoplasm, excluding operability. After Decker, only 5% of pleural effusions-associated lung cancer is paraneoplastic, making it possible for curative surgery [68]. Although there are signs suggesting the paraneoplastic nature of PE (the squamous type of lung cancer, low amount of pleural fluid, the presence of transudate, the association of pneumonia), thoracoscopy is the one that establishes the diagnosis and determines the outcomes of surgery.

Self-study

1. Which statement is/are true:
   a. transudates generally reflect a systemic disorder
   b. exudates signify usually the existence of a local pathology (pleuro-pulmonary pathology)
   c. Malignant PE in lung cancer may be ipsilateral or bilateral (bilateral metastases) and never contralateral or opposed side, or it is associated with pericarditis

d. MRI examination may be useful in the investigation of pleural mesothelioma.

2. Which statement are true:
   a. Thoracoscopic pleural biopsy allows to perform multiple targeted biopsies from lesions of the pleura, lung and mediastinum
   b. thoracotomy with pleurectomy should be considered as palliative therapy
   c. thoracoscopy is the one that establishes the diagnosis and determines the outcomes of surgery in the paraneoplastic PE.
   d. Malignant PE have poor prognosis

Answers

1. 1. Which statement is true:
   a. CORRECT
   b. CORRECT
   c. CORRECT
   d. CORRECT
2. Which statements are true:
   a. CORRECT
   b. CORRECT
   c. CORRECT
   d. CORRECT.

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Pleural Empyema

Silvia Ceccarelli, Valentina Tassi, Francesco Puma, and Lucio Cagini

Key Points

1. Parapneumonic empyema is the most common type of empyema and is often correlated to microbial invasion from contiguous areas, such as bacterial pneumonia, lung abscess and bronchiectasis.
2. The pathological progression of parapneumonic empyema has been classified into three stages: exudative, fibrinopurulent and organizing stage.
3. Chest X-ray, combined with other imaging studies like thoracic ultrasound and contrast-enhanced CT scan can help in discriminating between complicated and non-complicated pleural effusions. Diagnostic pleural fluid sampling should be performed in patients with pleural effusion and either sepsis or a pneumonic illness.
4. The main treatment objectives should be, the removal of purulent fluid from the pleural space and the re-expansion of the affected lung. These could be obtained by means of thoracentesis, pleural drainage or surgical debridment.

Introduction

Pleural infections afflict about 80,000 patients annually in the USA, with an incidence of about 9 per 100,000 [1, 2] and approximately 20–40% will undergo surgical interventions [3–5]. Pleural empyemas tend to be more frequent in childhood and elderly age [6]. Overall, the mortality rate at one year from diagnosis has been reported to be between 15 and 20% [7–9].

Historical Notes

Hippocrates in 500 BC reported a detailed description of pleural infection and its management with open drainage [4]. The use of closed-chest tube drainage was first reported by Bulau in 1875. The open technique remained the mainstay of treatment for many years and was associated with mortality rates of up to 70% [10, 11]. After World War I, when epidemic influenza caused the widespread Streptococcal pneumonia, the Empyema Commission published recommendations on the use of closed chest tubes, obliteration of the pleural space and nutritional

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support [4]. The adoption of the standard of care and the availability of antibiotics, led to a decreased incidence of empyema and therein its associated mortality [3].

Etiology

Parapneumonic empyema is the most common type (70%) and is often correlated to microbial invasion from contiguous areas, such as bacterial pneumonia, lung abscess and bronchiectasis [12–15]. Risk factors for its development are immunosuppression, drug abuse, diabetes mellitus, and the use of corticosteroids [7, 16–19]. Moreover, anaerobic bacteria empyema is often associated to poor dental hygiene, and result of aspiration phenomena due to gastroesophageal reflux, sedative drugs or alcohol abuse [4, 17].

Iatrogenic pleural infections account for 20% of all empyemas; after pneumonectomy this incidence has been reported to be as high as 12%, while, the rates after lobectomy and minor resections are lower. As well, after surgical procedures, these infections can derive from the esophagus, pericardium or subdiaphragmatic structures [3, 20, 21]. Finally, penetrating or blunt chest traumas, esophageal rupture or thoracentesis are also responsible for causing empyema. Pulmonary infarction, the aspiration of foreign bodies, head and neck infections have also been reported as etiological factors [22–24].

Microbiology

Before the advent of antibiotic therapies in the 1940s, the most common causative agents of pleural infections were Streptococcal and Staphylococcal species [5]. Recently anaerobes and Gram negative bacteria have emerged [25]. The microbiological spectrum depends on the setting of infection (community or hospital acquired), geographical location, age and immune status [6, 7, 26–28]. In the community acquired setting, Gram positive organisms are responsible for pleural empyema in 60–70% of cases, especially Streptococcal species and Staphylococcus Aureus. Streptococcus Milleri is reported to be the most common organism in community acquired empyemas worldwide [4, 15, 26, 27, 29]. Gram negatives, including Enterobacteriacae, Escherichia Coli and Haemophilus Influenzae, account for 9–17% of bacteria isolated; usually they are found in patients with comorbidities [26]. The remainder are due to anaerobes including Bacteroides and Poststreptococcus species [4, 17, 30, 31]. In the hospital acquired setting, Gram positive organisms are reported to be isolated in 50% of pleural cultures, with Staphylococcus Aureus being positive in over 40% of cases. Among these, MRSA may account for two thirds of cases [7, 28, 32]. Anaerobes and Gram negatives, including Escherichia Coli, Pseudomonas Aeruginosa and Klebsiella species, result being the causative agents in the remaining cases. Klebsiella species are reported to be the most common organisms isolated in pleural infections in the Far East [33–35]. In pleural empyemas secondary to anaerobes and Gram negatives, polymicrobial infection is common, especially in elderly patients with comorbidities [33, 36]. Pleural empyema due to fungal infection is rare, accounting for less than 3% of cases. Candida species are the most common isolated organisms and are almost exclusively observed in immune-compromised hosts [37, 38]. In large series, the offending microorganism could not be found with conventional methods in over 40% of pleural infections [3, 6, 7, 15]. When DNA amplification was applied, a further 10–15% of causative agents was identified. With pleural biopsy culture added to pleural fluid examination, an additional 30% of microorganisms responsible for pleural infection were observed [39–42].

Pathogenesis and Staging

In healthy subjects, the pleural fluid usually contains limited amounts of LDH, mesothelial cells, macrophages, lymphocites and proteins. The latter concentrations generally are similar to

those of the interstitial fluid. The pH is usually about 7.6. Pleural fluid contains lower levels of sodium, higher levels of bicarbonate and similar levels of glucose, compared to serum [14, 43, 44]. When a pathological process occurs, these parameters fall outside of range.

The pathological progression of parapneumonic empyema has been classified into three stages. The first of these is the exudative stage, which is characterized by a sterile parapneumonic exudate due to increased capillary vascular permeability [45, 46]. The production of α-TNF and IL-8 induce reactions in the pleural mesothelial cells which facilitate permeability [47, 48]. Pleural fluid in this stage is free-flowing with low white cell count, low LDH, normal pH and glucose, and it does not contain microbes and therein, may not respond to antibiotic therapy. The second stage is the fibrinopurulent stage, which occurs when organisms migrate into the pleural space as result of inappropriate treatment of stage I [4]. Here, inflammatory reaction promotes the migration of inflammatory cells and the activation of the coagulation cascade. Specifically, neutrophils in the pleural space increase the plasminogen activator inhibitors (PAI-1 and PAI-2) and decrease the tissue plasminogen activator (tPA) resulting in fibrin deposition [49, 50]. As a consequence, the pleural fluid tends to septate [51]. In this phase the lactic acid and the carbon dioxide, produced in the pleural space, determine pH and glucose reductions associated to high LDH levels. Pleural space drainage is usually required [52]. The third stage is the organizing stage, which is characterized by fibroblasts proliferation that changes the intrapleural fibrin membrane into thick, non-elastic pleural "peel" that encases the lung and contributes to the severe impairment of lung expansion [4, 53]. The production of pleural pus decreases here, but, whenever the pleural cavity is not adequately treated, the pus might either drain through the chest wall as empyema necessitatis, or produce a bronchopleural fistula [20, 44]. These three stages do not occur when the microrganisms invade the pleura from a hematogenous route or from extrapulmonary foci [3, 4].

Clinical Presentation

The clinical presentation of pleural empyema can be extremely variable. Commonly, these patients complain of dyspnea and pleuritic chest pain which are often accompanied by fever and cough [20, 21]. Physical examination is usually suggestive of pleural effusion, however a thorough anamnesis is necessary to assisting determining the underlying etiology. Most non-pneumonic empyemas indeed are iatrogenic [4, 5]. Regarding parapneumonic pleural effusions, the clinical picture depends on whether the causative agents of pneumonia are aerobic or anaerobic. Acute onset of chest pain, fever, sputum production and dyspnea in previously fit patients can be highly indicative of aerobic infection. In compromised patients with fatigue, suddenly weight loss, anaemia or anorexia, empyema typically takes a subacute course and the infective agents usually are anaerobic [54–56]. Fever and signs of sepsis, including an elevated white cell count and inflammatory markers, may indicate the progression of pneumonia to pleural empyema [4].

Pneumonia severity scores have been proposed to predict the risk of empyema onset. Variables included in these scores are: CRP, albumin and sodium levels, platelet count as well as alcohol and intravenous drug histories [57, 58].

Imaging Studies

With chest X-ray, a conspicuous pleural effusion is easily identified, whereas a small pleural effusion <175 ml is often missed, mostly at postero-anterior views [59]. Moreover, concomitant lung consolidations, especially if localized at the lower lobes, could be difficult to differentiate from pleural effusions. Thus, chest X-ray should be combined with additional imaging studies. Thoracic ultrasonography (US) has gained importance over the last years and, at present, is considered the cornerstone of imaging studies of pleural effusions. It is easily available and can be performed bedside, even by

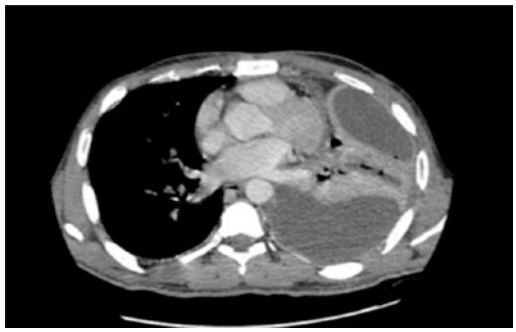

Fig. 1 CT scan of a patient with left-sided empyema. There is a thickened visceral and, partially, parietal pleura (split pleura sign) and a septated pleural effusion

non-radiologist clinicians, therein facilitating the diagnostic process. Thoracic US is effective in identifying small pleural effusions and estimating their volumes. Moreover, ultrasonographic patterns correlate with pleural fluid characteristics and homogeneously echogenic effusions are suggestive of either haemothorax or empyema [59]. Pleural thickening and septations can also be detected with ultrasonography, which suggest the presence of an exudative pleural effusion [60]. Contrast-enhanced CT scan with tissue phase can evidence lung parenchyma and suggests the causes of pleural empyema. Parietal pleural thickening is seen in more than 80% and pleural enhancement in almost 95% of empyema patients. Concurrent thickening and enhancement of parietal and visceral pleural can lead to the so-called "split pleura sign", present in about 70% of empyemas [61, 62] (Fig. 1). CT findings can help in discriminating between complicated and non-complicated pleural effusions [63]. Finally, mediastinal lymphadenopathy can be present in up to one-third of patients with empyema [4].

Blood Analysis

Pleural fluid analysis is able to assess the most significant parameters for complicated pleural effusions/empyemas. However, blood sampling adds important information: it can reveal increases in both the white cell count and C reactive protein level, which are suggestive of pleural infection progression. Moreover, a failure of the CRP level to be halved, may predict a high risk for developing empyema [4]. Regarding patients with community acquired pneumonia, risk factors include: albumin <30 g/dl; CRP >100 mg/l; sodium <130 mmol/l and platelet count $>400 \times 10^9$/l [57]. Finally, blood cultures result positive in approximately 14% of patients with pleural infections and often are the only opportunity to reliably obtain a positive microbiology [7]. Therefore, blood cultures should always be performed in patients with pleural infection [4].

Pleural Fluid Analysis

Pleural fluid sampling is recommended for patients with an effusion greater than 1 cm associated with either sepsis or pneumonic illness, or in cases of recent chest trauma or surgery [4, 21]. This sampling should be performed by ultrasound-guided thoracentesis. The aspiration of either purulent fluid or a positive Gram's stain or culture from pleural fluid, is by itself pathognomonic of empyema.

Patients with pleural infection will develop a pleural fluid acidosis associated with an increased LDH level and decreased glucose level. Whenever pleural fluid pH <7.2 chest drainage should be considered. The pleural sample should be collected anaerobically in a heparinised syringe; residual lidocaine or heparine may reduce pH, whereas air in the syringe may increase pH. Additionally, a LDH level >1000 IU/l and/or a glucose level <3.4 mmol/l have been suggested as the indication for performing chest drainage [4]. Pleural fluid samples should also be sent for microbiological analysis. Besides universal sterile containers, samples should also be collected in blood culture bottles, to improve the percentage of positive culture from 40% to almost 60% [64].

Treatment

The main treatment objectives should be the removal of purulent fluid from the pleural space and the re-expansion of the affected lung [65]. How to obtain these is a matter of debate as they mainly depend on the stage of infection.

General Instructions

Poor nutrition has been identified as an unfavourable determinant of outcome in patients with empyema. It has also been suggested that hypoalbuminemia correlates with a worse outcome [17, 66]. Moreover, pleural infection is responsible for catabolic consequences that can trigger immunodeficiency and therein slow recovery [67]. The risk of venous thromboembolism is high in patients diagnosed with empyema, thus thrombosis prophylaxis with heparin should be considered. Whenever anticoagulant treatment is not feasible, thromboembolic deterrent stockings or mechanical prophylaxis should be considered [4].

Antibiotics

Antibiotic therapy plays a fundamental role in the successful management of acute pleural empyema and it should be chosen on the basis of microbiologic analysis of both the pleural fluid and the blood culture. However, antibiotics are often started empirically, as soon as the pleural infection is diagnosed. Specifically, small effusions with a thickness <10 mm will generally resolve with empirically chosen antibiotics, but an increase in pleural effusion and a worsening of clinical conditions necessitate a re-evaluation of the antibiotics plan according to microbiologic analysis of the pleural fluid [44]. In fact, a randomised study reported that 54% of patients with pleural empyema had positive pleural fluid cultures and 12% had positive blood culture results; the latter often having no other positive microbiology results [29]. Nevertheless, up to 40% of empyema cases are culture negative. In these cases the choice of antibiotic therapy should include patient history along with any potential causes of pleural infection, especially community- or hospital-acquired [21]. Even if some variability can be encountered in the setting of the empirical antibiotic therapy, it is generally suggested, for the community-acquired empyema, the use of an aminopenicillin associated with a ß-lactamase inhibitor (e.g., amoxicillin + clavulanate, ampicillin/sulbactam) or the use a second-/third-generation cephalosporin (e.g., ceftriaxone) [21, 32]. Clindamycin is capable of adequately penetrating the pleural space, and in light of this, patients with allergy to penicillin can be treated with clindamycin alone or in association with either a cephalosporine or a fluoroquinolone [68].

In patients with hospital-acquired empyema, the increased risks of MRSA and Pseudomonas need to be weighed. In these cases vancomycin plus either piperacillin/tazobactam, or linezolid should be administred. Moreover, Tigecycline has been reported to be a reliable alternative [21, 32]. Aminoglycosides should not be utilised because they do not reach the pleural space and are inactivated by acidosis in the pleural fluid [69]. The use of intrapleural antibiotics is still debated. Although several studies have described positive results, none of them have been a randomised control trial [70, 71]. To date, no randomised studies have investigated for the optimal duration of antibiotic therapy in empyema patients. Despite this, it has been reported that antibiotic therapy should be administered from 2 to 6 weeks. A shift to oral therapy is generally indicated after improvements in both the clinical condition and the inflammatory markers. Results from a recent cohort study suggest that the prolongation of intravenous therapy, rather than oral therapy, may reduce the risk of treatment failure [72].

Thoracentesis

Diagnostic pleural fluid sampling should be performed in patients with pleural effusion and either sepsis or a pneumonic illness. This is because, it

is not clinically possible to differentiate a simple effusion that may resolve with antibiotics, from a complicated parapneumonic effusion that requires chest tube positioning [4, 73].

Pleural fluid characteristics need to be defined in order to plan the treatment management. Specifically, pleural fluid aspiration is indicated for patients with a pleural effusion >10 mm and pneumonia, clinical signs of either sepsis or recent chest trauma, or recent surgery. Thoracic ultrasound should be used to reduce the risk of pneumothorax, as well as any patient discomfort [74–76]. In patients with complicated effusions, therapeutic thoracentesis without chest drain placement is not indicated [21].

Chest Drainage

Tube thoracostomy with appropriate antibiotic therapy is the mainstay of treatment for stage I empyema. Whenever pus or turbid/cloudy fluid is present in pleural fluid samplings a chest tube should be promptly positioned. Another indication to chest drain positioning is when there is a complicated parapneumonic effusion, defined as a pleural fluid pH <7.2 and/or a bacterial invasion of the pleural space identified by positive Gram stain or positive pleural sample culture [77]. The radiologic appearance of the pleural collection might also influence management, as the presence of loculation on chest radiography or ultrasonography correlates with a worse outcome and may be an additional indication for early chest tube drainage. Moreover, a large pleural collection, occupying more than the 40% of the affected hemithorax, more frequently requires surgical debridement [78]. In these cases, chest drain should be positioned under radiologic guidance, given the risk of loculated effusion. Currently, there is no consensus on the optimal size of a chest tube. Although large-bore drains (≥28-F) have been more frequently utilised to facilitate the evacuation of pus or high viscosity fluids, a recent prospective, non-randomised study, did not show significant differences in the success rate with the use of tubes ≤14-F and tubes >14-F [79]. Additionally, in a large, multicentre randomised trial on intrapleural fibrinolytic therapy, a specific analysis did not reveal any improvement in terms of efficacy with large-bore, compared to small-bore tube [29]. As small-bore catheters (10–14-F) are easier to insert and are more comfortable for the patient, their use is recommended as initial treatment for pleural infections. The leading causes of drain failure include occlusion and dislodgement. Regarding the management of chest tubes, several studies have evidenced that regular flushing (20–30 ml of saline every 6–8 h via a three-way tap) and application of suction (−20 cm H_2O) can improve drainage efficiency and therein avoid catheter occlusion [4]. A chest tube can be removed when both clinical signs of sepsis are solved and radiologic results indicate a reduction in the pleural collection. Finally, in patients with chronic pleural space infections who are unfit for surgery, long-term tube thoracostomy in association with antibiotic therapy could be a therapeutic option [80].

Intrapleural Fibrinolytic Therapy

The fibrinopurulent phase (stage II) of empyema is characterised by fibrinous septations and elevated density of the pleural fluid. Over the past decades, intrapleural fibrinolytic drugs have been included in the management of both empyema and complicated pleural effusions. This procedure was first described in 1949 by Tillett et al. employing streptokinase, but it was characterised by immunological side effects, probably due to contamination during production, leading to its discontinuation [81]. Purified streptokinase and urokinase, available since the late 1980s, were used even though a clinical benefit was not demonstrated. In 2005, a double-blind, randomised multicentre trial (MIST-1) was published, that compared the clinical outcome of 430 patients with complicated pleural effusion treated with streptokinase (250.000 UI) or a matching placebo. The results suggested that intrapleural streptokinase did not reduce mortality, the frequency of surgery, the hospital length of stay or improve residual abnormality

on either the chest X-ray or dynamic lung volumes [29]. Currently, streptokinase and urokinase can be beneficial in breaking down fibrin septations, but they have no effect on fluid viscosity or in preventing formations of bacterial biofilms. Subsequently, data regarding the use of nebulized DNAse in the treatment of cystic fibrosis patients with highly viscous secretions were derived [82]. In 2011 the results of MIST-2 that was a blinded, 2-by-2 factorial trial were published suggesting a synergic association between DNAse and fibrinolytic therapy. The study reported that the association between tissue plasminogen activator (t-PA) and DNAse lead to a statistically significant benefits in terms of absolute reduction in chest X-ray opacification, hospital length of stay, frequency of surgery and mortality. Neither t-PA nor DNAse alone were associated with better results, suggesting an effectiveness from only the combination therapy [83]. Bleeding has been associated with the use of intrapleural fibrinolytic therapy, however it has been reported that systemic bleeding is improbable and the incidence of local bleeding is low [84]. The use of intrapleural fibrinolytic therapy is not recommended as part of standard care for empyema patients; however, it is suggested for patients not suitable for surgical treatment (Fig. 2) [4, 21, 73].

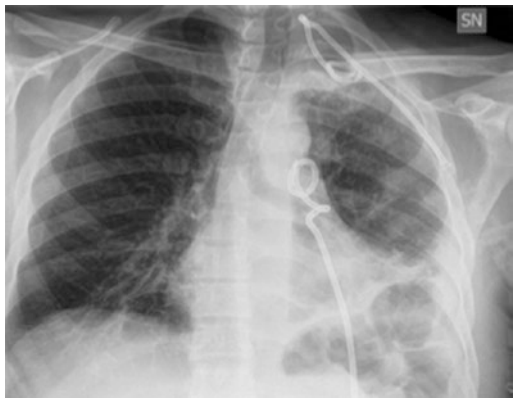

Fig. 2 Chest X-ray of a patient with a left-sided, multiloculated, pleural empyema unfit for surgery, successfully managed with intrapleural fibrinolytic therapy (urokinase) through two small-bore catheters (12-F)

Surgical Management

In patients with stage II-III empyema, surgery is the mainstay of treatment [21, 73]. Generally, surgical treatment is indicated for the following patients: those with stage III empyema, those with early-stage empyema whenever there is a failure of medical treatment (Fig. 3), and those with complicated pleural effusions. Effectiveness of treatment is usually verified 5–7 days from the start of therapy. Failure is defined as the worsening of clinical signs associated with sepsis and/or residual pleural effusion on imaging [4]. The main objectives of surgical treatment should be the evacuation of the infected material, debridement of pleural septations and the re-expansion of the affected lung (Figs. 4 and 5). In cases of stage III empyema, the latter condition can require pleural decortication, that is the removal of the thickened, restrictive visceral pleura. To ensure the expansion of the lung it is crucial to obtain both a resolution

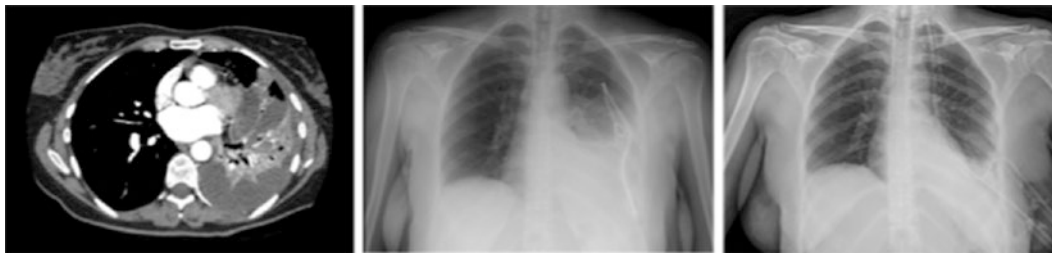

Fig. 3 Patient with left sided pleural empyema successfully treated by means of pleural debridement and partial pleural decortication in videothoracoscopy after a failed attempt of conservative treatment through small-bore catheters. Preoperative CT scan (**a**), chest X-rays after drainage insertion (**b**) and after surgery (**c**)

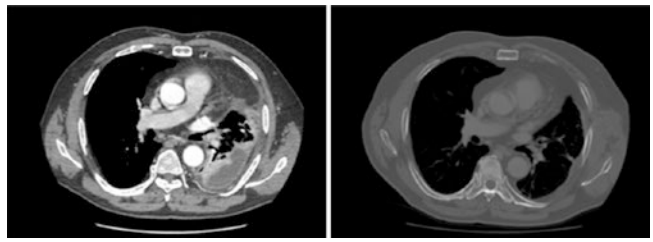

Fig. 4 CT scan of a patient with left-sided empyema before (**a**) and after (**b**) surgical treatment: pleural debridement and partial pleural decortication through left videothoracoscopy

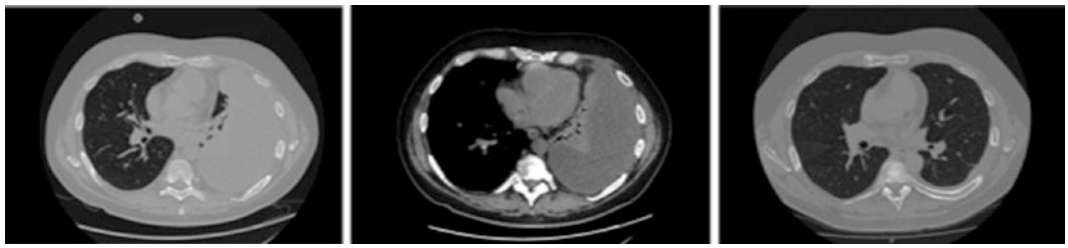

Fig. 5 CT scan of a patient with left-sided empyema before (**a**–**b**) and after (**c**) surgical treatment: pleural debridement and pleural decortication through left minithoracotomy

of the infection and a reduction of the air leak, which is always present after a decortication procedure [65]. The most effective methods for achieving these targets are still a matter of debate. In fact, clinical conditions, the stage of empyema and the preferences of the surgeon all play important roles. In the past, open thoracotomy was the only approach for stage III empyema. Presently, video-assisted thoracoscopic surgery (VATS) is usually proposed as the first-line surgical approach [3, 73, 85]. In support of this practice, a recent meta-analysis compared the results of VATS decortication with open surgery. The Authors reported that VATS resulted being equivalent to open surgery in terms of resolution of disease and superior in terms of hospital length of stay, postoperative complications and morbidity [86]. Complete lung decortication remains a highly challenging and time-consuming procedure that requires the surgeons to be experienced in VATS surgery [87]. The choice of which VATS technique should be used mainly depends on the preference of the surgeon; encouraging results have been reported also with uniportal thoracoscopic decortication for well-selected patients [88]. The requirement of intraoperative conversion from minimally-invasive to open approach remains controversial. Factors that seem to be associated with a greater risk of conversion include the stage of empyema and the time from the beginning of clinical manifestations [53]. Other parameters that may influence the need for conversion are male gender, post-pneumonic empyema and Gram-negative germs [89]. Early surgical indication is deemed to be the most important factor influencing the conversion from VATS to open surgery [73].

Thoracostomy and Space-Filling Techniques

Incomplete re-expansion of the affected lung may necessitate the execution of manoeuvres targeted to the obliteration of the residual pleural space and the prevention of any reaccumulation of the infected fluid. The most frequently used procedures include myoplasty, open thoracic window, pleural tenting and pleuroperitnoeum [21, 90]. Pedicled muscle flaps usually use latissumus dorsi, serratus anterior, trapezius, rhomboid and the perctoralis major. Complex muscles flaps can be realized using lower

abdominal muscles, but they should be reserved for patients with unavailable chest wall musculature. A failure rate of 25% has been reported when myoplasty is performed in a heavily infected environment [21, 73]. Omentum flaps can also be prepared: they are characterized by elevated healing capacity, but need an abdominal access to be harvested, and this can extend infection to the abdomen [21].

Open thoracic windows can be indicated in those patients with chronic empyema who are deemed unfit for surgical decortication or after failure of other surgical procedures. Thoracostomy should include at least 2–3 segments (5–6 cm in length) of ribs in the lateral portion, then the parietal pleura should be sutured to the skin edges [73, 91]. Wet dressings of povidone iodine (solution diluted 20:1) should be changed once daily. An alternative to dressing changes is vacuum-assisted closure (VAC) that requires the packing of the pleural space with polyurethane foam and the application of a suction (−25/−75 mmHg adjusted on the basis of signs of mediastinal traction). Recent studies have suggested that the use of a VAC device may reduce the duration of open thoracic windows, and therein decreasing morbidity and length of hospital stay [92].

Self-study

1. Pleural infection will develop the following modifications in the pleural fluid:
   A. acidosis, increased LDH level and decreased glucose level;
   B. acidosis, normal LDH level and normal glucose level;
   C. alcalosis, increased LDH level and decreased glucose level.
2. Which statement is false?
   A. Tube thoracostomy with appropriate antibiotic therapy is the mainstay of treatment for stage I empyema.
   B. In patients with stage II–III empyema, surgery is the mainstay of treatment.
   C. Surgery is always indicated, regardless of the stage of empyema.

Answers

1. Pleural infection will develop the following modifications in the pleural fluid:
   A. acidosis, increased LDH level and decreased glucose level; CORRECT
   B. acidosis, normal LDH level and normal glucose level;
   C. alcalosis, increased LDH level and decreased glucose level.
2. Which statement is false?
   A. Tube thoracostomy with appropriate antibiotic therapy is the mainstay of treatment for stage I empyema.
   B. In patients with stage II–III empyema, surgery is the mainstay of treatment.
   C. Surgery is always indicated, regardless of the stage of empyema. CORRECT

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Chest Tube

Alberto Matricardi, Valeria Berti, Alberto Italiani, and Lucio Cagini

Key Points

1. Chest drainage is a procedure with a high benefit/cost ratio and a low complication rate.
2. Small caliber chest tubes (≤20 Fr), instead of large-bore ones (≥20 Fr), are easier to insert, even at bedside, and less painful during and after the procedure.
3. Small-bore chest tubes are mostly used to treat primitive pneumothorax and malignant pleural effusion. Conversely, large-bore chest tubes are preferred for hemotorax, pneumothoraxes in intubated patients, and for patients with empyema.
4. Pain, drain dislodgement and blockage, infections and, rarely, visceral injury may complicate the chest drain positioning. A proper training and an evaluation of the risk factors should be done to reduce this events.

Introduction

Chest drainage is commonly used in pleural settings, and its overall associated complication rate is reported to be low. While, its benefit/cost ratio is high, particularly with the use of CT-scan or thoracic ultrasound. In this chapter we describe the recommended sizes and types of tubes for the currently used chest tube insertion methods.

Chest Tube Sizes and Types

Chest tubes can be divided into two categories: large and small-bore (Fig. 1).

Each category has its own characteristics and method of insertion. To determine the appropriate size of the chest tube to use, the features of the drained material and the filling speed must be considered.

The drainage of the pleural cavity follows the physical laws of any cylindrical tube. Poiseuille's law and the Fanning equation state: flow is a function of tube radius, pressure, viscosity, friction and length. Large radius tubes are thought to drain fluid and air better from pleural spaces. However, many studies have investigated the flow of the chest drain according to both the size of chest tube utilized and pleural fluid viscosity. These results have suggested that the size of the tube is determining, especially for catheters smaller than 8 Fr, or when a stopcock or Luer-Lok connector is used [1–3]. Over the past two decades, there has been a tendency to prefer small caliber chest tubes (≤20 Fr) [4, 5] over large-bore ones (≥20 Fr). The advantages of the former include, they are easier to insert,

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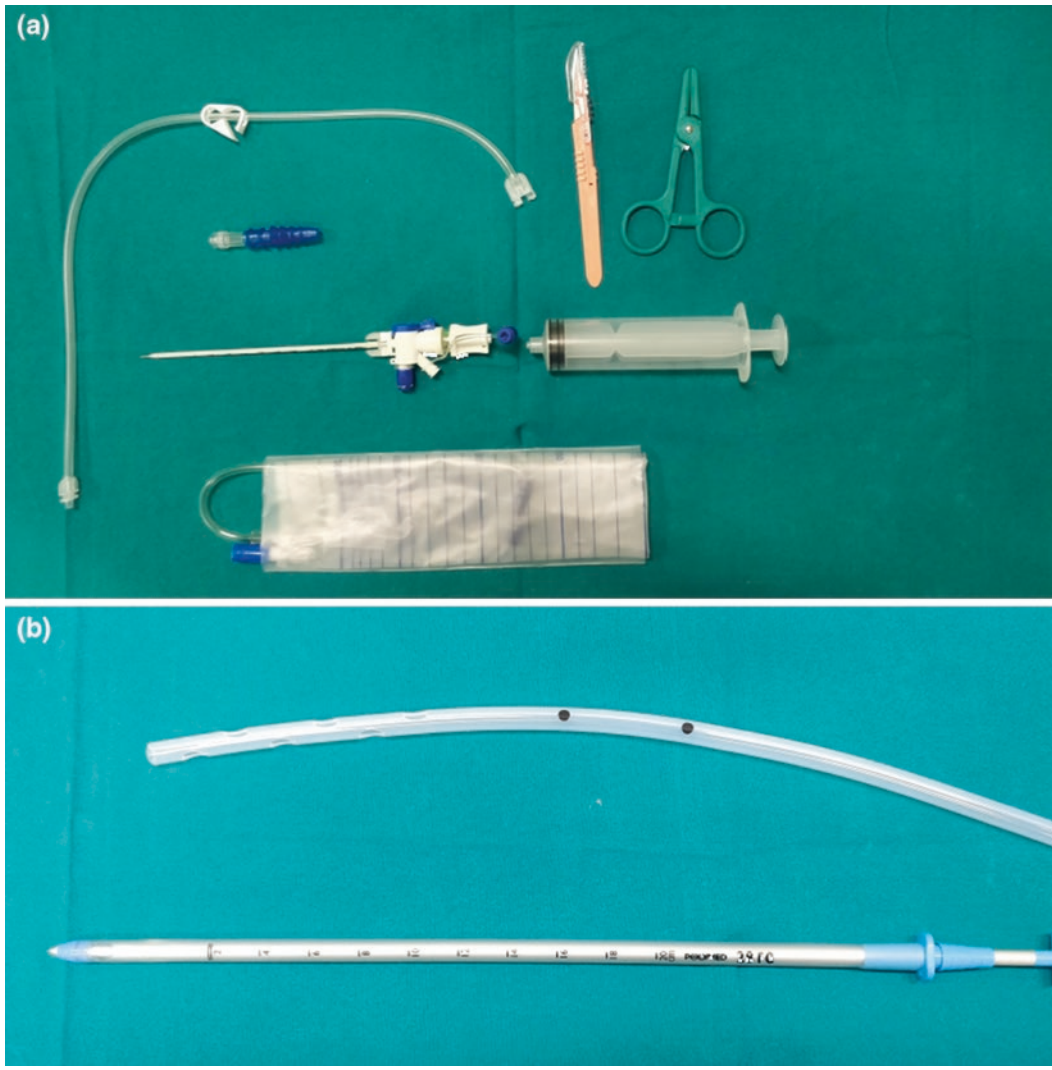

Fig. 1 Chest drainages: an example of a small-bore chest tube kit (**a**) and a large-bore chest tube (**b**)

even at bedside, and less painful during insertion and thereafter [6]. Small-bore catheters can be used to treat pneumothoraxes, malignant/chronic effusions, as well as simple uncomplicated empyemas (Stage I) [7]. Moreover, the use of small bore tubes has been associated with lower rates of overall associated complications, particularly for malposition or injuries to neighbouring tissues. These rates have been reported to be even lower when using ultrasound or CT guidance [8, 9]. Conversely, large-bore catheters are often preferred in cases of large, high-viscosity pleural effusion such as hemothorax, or in cases of high-volume air leaks, including pneumothoraxes in intubated patients [6].

Indications

Pneumothorax

According to the British Thoracic Society, eligible patients include those affected by primary or secondary spontaneous pneumothorax, as well as

those with pneumothorax of any size plus dyspnoea. To relieve the dyspnoea, a needle (14–16 G) aspiration should be attempted. In cases of recurrence, a small-bore chest drain insertion should be performed; which has been reported to have a success rate similar to that of larger drains [10, 11]. Moreover, this approach also permits a "stepwise" management of spontaneous pneumothorax, culminating with the surgical intervention, whenever a persistent air leak or an incomplete reexpansion of the lung is recorded. Whereas, tension pneumothorax, bilateral pneumothorax and hemopneumothorax are life-treating conditions that require an immediate chest tube placement. In these cases, large-bore chest tubes (>20 Fr) are often appropriate [12]. Furthermore, in cases of persistent air leak, and to further both the lung reexpansion and the apposition of the pleural layers, a suction between -10 *and* $20\ cm\ H_2O$ may be applied. Whereas, small pneumothoraces (<2 cm) without any evident respiratory symptoms, may be managed with bed rest and oxygen to foster the "nitrogen washout".

Malignant Pleural Effusions

In the case of malignant pleural effusion, as the main priority should be to achieve an adequate palliation of the diagnosed symptoms, a chest tube could be indicated. Likewise, a chest tube can also be utilized to instill pleurodesic agents, such as slurry talc or bleomycin. In face of recurrence, the placement of an indwelling chest tube should be considered. This type of drainage need to be anchored by tunneling a small cuff subcutaneously and thereafter a one-way valve is connected at the end; allowing for at home or in ambulatory use. Furthermore, the use of indwelling chest tubes is associated with spontaneous pleurodesis in about 46% of patients [13, 14]. However, it is associated with a risk of infection between 0% to 12%, mainly *S. Aureus* [15, 16]. This overall risk of infection can be minimized by performing thoracoscopic poudrage talc: reductions in chest tube duration and hospital stay have been reported, leading to an improved quality of life [17].

Complicated Parapneumonic Effusion and Empyema

The incidence of pleural infection (complicated parapneumonic effusion and empyema) is on the rise for all ages groups, worldwide [18]. Despite advances in diagnostics and treatment, the 1-year mortality rate for adults remains above 20%, and can reach up to 30% for the elderly with comorbidities [19, 20]. Therefore, a prompt effective treatment needs to be carried out after having appropriately assessed known risk factors. The pathological progression of pleural infection can classified in clinical stages (I-II-III): (1) exudative stage with no detectable bacteria and absent of any microbiological or biochemical evidence of bacterial invasion, (2) the fibrinopurulent stage in which bacteria invade the pleural space and therein a production of fluid loculation and pleural adherences, (3) the organizing stage where fibroblast occur with the formation of a thick anaelastic peel on both pleural surfaces. Prognostic factors that should be considered in the decision on whether to place a chest tube: (1) the presence of pus in the pleural space, (2) positive Gram staining of the pleural fluid, (3) a pleural fluid glucose level below 40 mg/dl, (4) positive pleural fluid culture, (5) pleural fluid pH < 7.0; (6) pleural fluid LDH > 3 x above the normal limit for serum, and (7) loculated pleural effusion [20]. When the pleural fluid appears as thick pus or either the Gram stain or culture is positive, a franckly empyema is present and the chest tube positioning is mandatory [19–22].

In these cases, a large-diameter drainage tube (>24 Fr) is should be placed. Although in 2010, the British Thoracic Society guidelines indicate that a small-bore catheter (10–14 Fr) is adequate for most cases of complicated parapneumonic empyema, because it has been associated to less discomfort for the patient. Being so, regular flushing with the instillation of 20–30 mL saline every 6 h, via a three-way stopcock, is recommended.

Intrapleural fibrinolytic agents have been used to increase the volume of pleural fluid drainage, as they can reduce the formation of

multiple septation. However, the largest randomized clinical study to date, has reported that streptokinase application in the pleural cavity is not associated with a reduced hospital stay, the frequency of surgery or a lower mortality rate [21]. For this, the routine application of a fibrinolytic agent is not recommended [22].

Haemothorax and Chylothorax

Most haemothoraces are due to penetrating or non-penetrating chest trauma, while less often due to pleural malignancy, anticoagulation or several other disease states. When a diagnostic thoracentesis reveals bloody pleural fluid, a hematocrit of the effusion needs to be obtained (fluid hematocrit $\geq$ 50% blood hematocrit). Specifically, a large-bore chest tube placement is recommended. In doing so, it can also decrease the incidence of subsequent empyema; as the presence of blood in the pleural space is a good culture medium [4]. Moreover, the collecting system allows to quantify the rate of bleeding; in cases of pleural hemorrhage (bleeding rate $\geq$ 200 ml/h with no signs of slowing) a prompt thoracotomy and/or VATS is necessary.

Chilotorax is frequently treated with chest tubes to alleviate dyspnoea (as the pleural fluid tends to collect rapidly) and to estimate the pleural fluid rate. To date, there have been no randomized controlled studies comparing large-bore and small-bore chest tubes for efficacy. Nevertheless, chyle is a viscid fluid associated with an overall low-rate of infection and small-bore chest tubes might be able to drain adequately [4].

Chest Tube Insertion

All operators performing this procedure need to be properly trained, and this should include a theoretical component highlighting its associated risks [23]. Clinical assessment must include any risk factors associated with minor and major complications. Most often, the chest tube is positioned in the "Triangle of safety", that is delimitated anteriorly by the lateral margin of the pectoralis major, posteriorly by the lateral edge of the latissimus dorsi and inferiorly by the fifth intercostal space. For a better exposure of the triangle area, the patient should be positioned on a bed, semi-reclined with his/her ipsilateral hand behind the head. Sometimes, in cases of apical pneumotohorax, the second intercostal space on the mid-clavicular line is chosen. However, this site of insertion is not routinely recommended for an augmented risk of injuries to the adjacent vascular structures. Prior to insertion, an explorative puncture using a small calibre needle is recommended in order to determine an appropriate point of insertion. Moreover, the needle puncture can also permit the injection of the local anesthesia [23].

The most frequently utilized techniques for placing chest tubes are: the Seldinger procedure with its guided wire and dilators, the trocar-tube thoracostomy and the operative tube thoracostomy [24]. The Seldinger procedure is the most popular technique, due to the fact that it is the easiest to perform. Specifically, a needle attached to a syringe is introduced into the pleural space and the expected content is aspirated to confirm the intrapleural position. A guided-wire is inserted into the needle and directed to the desired location. The needle is then removed and a small dilator is slid over the wire and gently inserted into the pleural space. After a few passages with progressively thicker dilators, a chest tube is advanced around the wire, following the path into the pleural cavity. The Seldinger technique is more frequently used to insert small-bore pleural catheters (<20 Fr), and no dilatation is needed for the smallest (<12Fr).

Whereas, trocar-tube thoracostomy is a blinded chest tube placement. A 2–4 cm skin incision parallel to the upper border of the inferior selected rib is performed after local anesthesia. Therein the chest tube, with a trocar positioned inside, usually a large-bore one, is pushed through the chest wall into the pleural cavity and finally the inner trocar is removed. The clamping of the tube, until the drainage system is attached, is necessary to prevent pneumothorax. This technique is associated with high

complication rates, especially when it is used to evacuate post-traumatic hemothorax in emergency settings [25].

Operative tube thoracostomy is commonly used for large-bore chest tube placement (>20 Fr). However, this procedure has been reported be painful despite the use of a local anesthesia. Therefore, the concurrent administration of low-dose of sedative is often recommended. The local anesthesia is injected and the incision is performed, as in the trocar procedure. Specifically, using a blunt scissors or a haemostat, the subcutaneous and muscular tissues just over the rib are spread and the parietal pleura is penetrated by pushing gently into the pleural space. The surgeon can insert his/her index finger inside the pleural space, palpating the adjacent structures and exclude the presence of any pleural adherences. The tube should then be advanced apically in cases of pneumothoraces and basally for pleural effusion and finally sutured in place. In conclusion, a chest radiography should be performed after every chest tube positioning, in order to exclude misplacement. Rarely is a CT scan needed to determine the location of the chest tube in the pleural space, or to determine why the chest tube is not able to drain adequately [26].

Complications

Pleural tube placement is a routine procedure not free of risks. In fact, the overall rate for early (<24 hrs post-placement) chest tube complications is approximately 3%, while for late complications (>24 hrs post-placement) this rate is between 8 and 10% [27]. To reduce these rates, a safety check-list needs to be compiled before the procedure, in order to minimize the incidence of wrong-side procedures, and highlight comorbidities and risk factors. In cases of pleural effusion, thoracic ultrasound is widely use for assuring a correct placement [28, 29]. For both early and late tube placement, malpositioning is the most frequently reported complication; particularly in urgent and emergency setting or whenever performing the trocar-tube technique [30]. The most frequent chest tube misplacement sites include the intraparenchymal, the fissural, the chest-wall and other tube placement sites. CT scan is considered the most reliable procedure for evidencing the precise location of the drainage. In fact, intraparenchymal tube placement is associated with potentially high injury risks for the large vessels and/or the lung parenchyma. This event is frequently due to pleural adhesions or pre-existing pulmonary disease; clinically it may be silent or confused with the pre-existing pleural disease, as in the case of secondary pneumothorax and massive air leaks. Rarely is a surgical procedure needed to repair the injury, but this should be evaluated according to the clinical and radiological presentation.

The placement of the tube in the fissure is frequent. In addition, no clinical differences have been reported in terms of duration of tube placement, need for a second drainage and length of hospital stay, compared with tubes properly placed [31]. However, whenever the interlobar/intrafissure location compromises the lung re-expansion, chest tube repositioning must be considered. Placement of a tube in the chest muscles wall is a rare and often innocuous complication; with a reported incidence of 1–1.8% [32]. Multiple rib fractures with chest-wall instability and emergency conditions are reported to be the major risk factors for this. Other-sites of tube misplacement include the mediastinal and the abdomen. The former is a rare situation possibly resulting in nerve, heart and large vessel injuries or esofageal perforation [27]. When the heart or large vessels are involved, a continuous stream of blood flows through the chest tube and this can induce marked hypotension, haemorrhagic shock and even death. Predisposing factors include thoracic deformities, enlarged cardiac chambers, trauma and emergency respiratory conditions [33]. The most common nerve injuries can afflict either the phrenic nerve or the sympathetic chain in the apex. The former can trigger a diaphragmatic paralysis, whereas the latter is associated with the Horner's syndrome (miosis, ptosis, hemifacial anhidrosis, and enophthalmos).

Esophageal perforation following tube thoracostomy is most often reported after esophageal surgery [34]. Pathognomonic signs include salivary or enteric contents passing through the chest tube. When one of these signs is present, a radiological esophagogram with contrast needs to be performed.

Abdominal placement of a chest tube usually occurs when the catheter has been positioned too low. Patients conditions such as obesity, diaphragmatic relaxation or post-traumatic diaphragmatic rupture can raise the risk of this event. In these cases, all of the intra-abdominal organs are at risk of injury. Specifically, when the liver or the spleen is involved, hemoperitoneum and hemorrhagic shock may occur. Whenever there is a stomach or bowel perforation, prompt surgical repair and an adequate antibiotic therapy is necessary to avoid peritonitis and sepsis [27].

Reexpansion Pulmonary Edema (REPE) is a rare complication that can occur when a chest tube is placed for pneumothorax or massive pleural effusion. It is associated with a mortality rate of up to 20% [35]. This pathogenesis is poorly understood, but increased endothelial permeability and loss of integrity of the alveolar capillaries seem to be implicated. REPE usually occurs on the same side of the reexpanded lung, but cases of REPE contra-laterally or bilaterally have been reported [35–38]. Major risk factors include young age (<40 years), collapse of the affected lung for more than 3 days, large pneumothorax (>30% of single lung), significative suction negative pleural pressure and a lung reexpansion too rapid [39].

Chest tube dislodgement after insertion and its blockage during the permanency is a common occurrence, mostly associated with the use of small-calibre chest catheters (<20 Fr). Kinking, angulations, blood clots or fibrin debris inside the tube may compromise functionality, especially in cases of trauma or infectious pleural disease [25]. An appropriate anchoring of the tube must be performed immediately after insertion and daily lavages are required when utilizing small-bore tubes, in order to ensure a correct functioning. Regarding large-bore tubes, milking or stripping can be used to unblock blood or fibrin clots, however these procedures have been associated with tissue entrapment, increased bleeding, and even left ventricular dysfunction [40–42].

Self-study

1. Which of these structures doesn't delimit the "Triangle of safety"?
   (a) Lateral margin of the pectoralis major
   (b) Second intercostal space
   (c) Lateral edge of the latissimus dorsi
   (d) Fifth intercostal space.
2. Which statement is true:
   (a) When the pleural fluid appears as pus or either the Gram stain or culture is positive, the chest tube positioning is mandatory.
   (b) The routine application of a fibrinolytic agent in the pleural empyema is recommended.
   (c) Reexpansion Pulmonary Edema (REPE) is a common complication with a low mortality-rate.
   (d) Trocar-tube thoracostomy is a safe procedure especially in emergency settings.

Answers

1. Which of these structures doesn't delimit the "Triangle of safety"?
   (a) Lateral margin of the pectoralis major is the anterior border
   (b) Second intercostal space CORRECT
   (c) Lateral edge of the latissimus dorsi is the posterior border
   (d) Fifth intercostal space is the inferior edge.
2. Which statement is true:
   (a) When the pleural fluid appears as pus or either the Gram stain or culture is positive, the chest tube positioning is mandatory. CORRECT
   (b) The routine application of a fibrinolytic agent in the pleural empyema is not recommended because they are not associated with a reduced hospital stay or a lower mortality rate.

(c) Reexpansion Pulmonary Edema (REPE) is a rare complication with a mortality-rate up to 20% that can occur when a chest tube is placed for pneumothorax or massive pleural effusion.

(d) Trocar-tube thoracostomy is associated with high complication rates, especially when it is used to evacuate post-traumatic hemothorax in emergency settings.

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Approaches and Surgical Techniques in the Pleural Tumors

Ahmet Erdal Taşçı, Ali Yeginsu, and Mustafa Vayvada

Key Points

- The solitary fibrous tumor of the pleura is rare and growing quite slowly tumor that is considered to be originated from subepithelial mesenchymal layer.
- The majority of these tumors arise from the visceral pleura with a pedicle. It is rarely observed in the lung parenchyma, pericardium, mediastinum, upper airway and extrapleural tissues.
- Patients are frequently asymptomatic. Symptoms can be seen due to localization such as cough, shortness of breath, chest pain.
- A definitive diagnosis of the tumor removed can be reached by histopathological and immunohistochemical examination.
- The most important treatment for solitary fibrous tumor is complete en bloc resection.
- Patients should be followed for a long time because it may recur even after many years.
- MPM develops as a result of the inhalation of asbestos or erionite, which are mineral fibers.
- Patients' occupation questioning is very important.
- The patient who has a history of asbestos contact should be aware of the risk of mesothelioma disease if there is a complaint of side pain and/or shortness of breath.
- If a patient with asbestos exposure has pleural fluid or pleural nodular involvement/thickening on the chest radiograph, the MPM concern should be considered.
- PET-CT is a more appropriate method for the evaluation of distant metastasis and mediastinal lymph node.
- MRI is more sensitive in demonstrating chest wall, diaphragm and pericardial involvement.
- Medical thoracoscopy or videothoracoscopy is the recommended diagnostic method for the diagnosis of MPM.
- Surgical technique are decided after preoperative radiology, clinical staging and finally intraoperative exploration.
- Pleurectomy is a complete pleural resection of the gross tumor tissue in the thorax. Radical pleurectomy is resection and reconstruction of diaphragm and/or pericardial in addition to pleurectomy.
- EPP should be performed in patients with appropriate prognostic characteristics, histology and stage.
- Multimodal treatment is an effective treatment that can achieve long-term survival in patients with early stage epithelial type MPM.

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Solitary Fibrous Tumors of the Pleura

Solitary fibrous tumors of the pleura (SFTP) account for 5% of all pleural tumors. SFTP was originally considered to be originated from the mesothelial layer; however, specific immunohistochemical staining and electron microscopy findings helped its reclassification as having a mesenchymal origin [1]. Approximately 80% of SFTPs are originated by the parietal pleura, whereas 20% originate from the visceral pleura [2].

Pathology

Solitary fibrous tumors are usually diagnosed as a result of immunohistochemical examination of the surgically removed specimen. In terms of gross pathology, solitary fibrous tumors are usually encapsulated, soft, and vascularized lesions. Histologically, these tumors have a characteristic appearance: a cellular appearance and an irregular distribution of spindle cells within the prominent collagenous stroma. Some regions of the tumor are cell-rich, while some regions are observed to be cell-poor [3] (Fig. 1).

Although these tumors are mostly benign, they can also be malignant. The criteria for malignancy are high mitotic activity, nuclear pleomorphism, increased cellularity where nuclei are intermixed, the presence of necrotic or hemorrhagic areas, and stromal or vascular invasion. Although these tumors are large, they are usually treated with simple excision, and the risk of recurrence is minimal if resection is done microscopically [4]. It has been found that approximately 12% of SFTPs are malignant and cause death due to local recurrence or metastatic disease [5].

Localized fibrous tumors have been reported to be involved in extrapleural tissues such as meninges, nasal cavity, oral cavity, pharynx, epiglottis, salivary gland, thyroid, breast, kidney, bladder, and spinal cord [6].

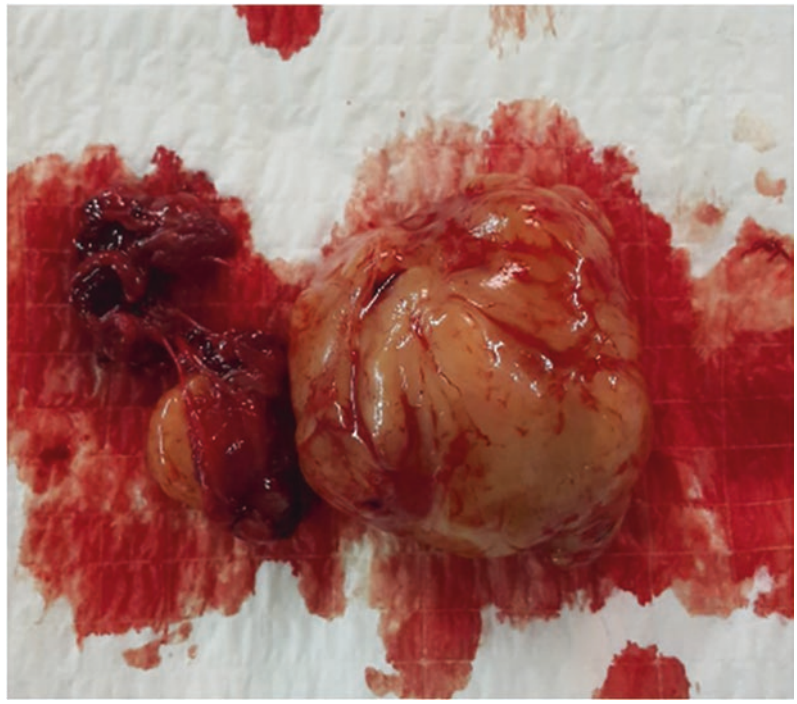

Fig. 1 Gross pathology of resection SFTP

Clinical Findings

The prevalence of these tumors is similar in males and females. SFTPs occur in all age groups but are most commonly observed in people aged 50–70 years [7]. They are not associated with genetic susceptibility and exposure to asbestos, tobacco, or other environmental agents.

Clinically, SFTPs are mostly silent for many years. They are mostly asymptomatic and usually discovered incidentally during chest X-ray examination. When these tumors become large, most patients with SFTP become symptomatic. Approximately 54–67% of patients with benign SFTPs have symptoms, while 75% of patients with malignant SFTPs are symptomatic [8, 9].

SFTP may present with various symptoms such as intrathoracic symptoms (dyspnea, chest pain, hemoptysis), systemic symptoms (hypoglycemia, hypertrophic osteoarthropathy), or nonspecific symptoms (fever, weight loss, fatigue). Hemoptysis and obstructive pneumonia are rarely seen as a result of airway obstruction. Chest pain is more common in patients with tumors in the parietal pleura. Clubbing, hypertrophic pulmonary osteoarthropathy, and refractory hypoglycemia may be seen as paraneoplastic lesions [10].

Radiology

Typically, chest X-ray reveals a well-defined, lobular solitary nodule, or mass in the pleural-associated lung periphery or fissure. Pediculated tumors are observed in fluoroscopy to be mobile or in different forms in the pleural space in inspirium and expirium as the patient's position changes [11]. Solitary fibrous tumors may mimic the solitary pulmonary nodule radiographically but often appear as lesions that do not show pleural-based chest wall invasion [12].

SFTPs mostly affect the middle and inferior hemothorax. They have a slow growth trend and can reach very large sizes. Large lesions and those originating from paramediastinal pleural surfaces are characterized by typical radiographic features of the pulmonary or mediastinal masses [13].

In computed tomography (CT), they typically appear as homogenous, well-defined, noninvasive, lobular soft tissue masses associated with a pleural surface (Fig. 2). They can create

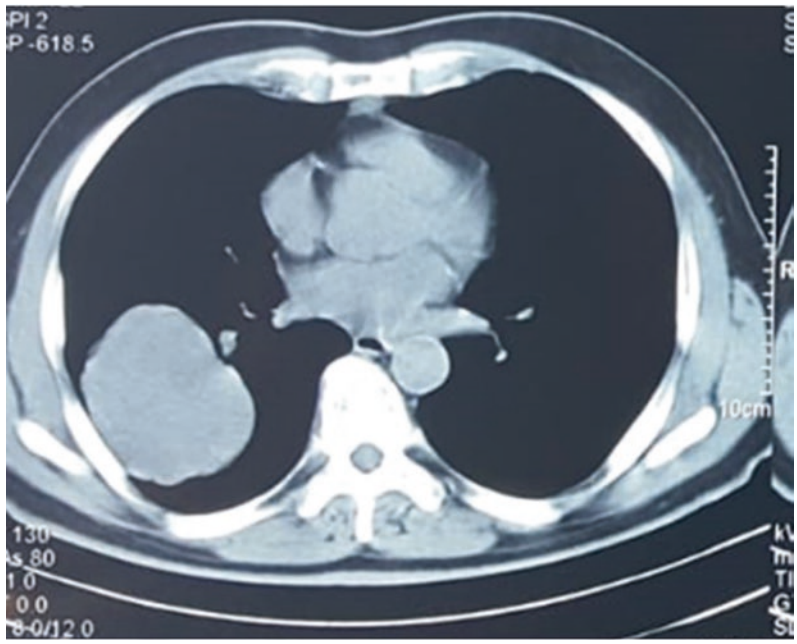

Fig. 2 CT findings of SFTP

a wide angle with the adjacent pleura or be located in the fissure [11]. While small lesions appear to be homogenous, large lesions may be heterogeneous due to cystic necrosis and bleeding. Larger lesions are typically heterogeneous and may not show CT features associated with focal pleural tumors. It may be difficult to differentiate the tumors of intraparenchymal origin seen in the interlobar fissure [14]. Calcifications may occur in benign or malignant tumors, and it may be difficult to distinguish these from bronchial carcinoid tumors. CT findings may not allow the differentiation of fissural SFTP from a peripheral lung lesion or the differentiation of an abdominal tumor when inferior hemithorax is affected [15]. Atelectasis, mass effect on the mediastinum and pleura, and pleural effusion are more common in malignant SFTPs than in benign tumors. Calcification is documented in 7% of cases, mostly in large lesions associated with necrosis [16]. Local invasion is rarely reported, and lymphadenopathy is not a feature of SFTP. Chest wall involvement is revealed by CT, and it occurs as sclerosis or pressure erosion in adjacent ribs [17].

Only a few magnetic resonance imaging (MRI) studies have reported the characteristics of SFTPs. MRI has a limited use in the evaluation of pleural disease. MRI may be better than CT to describe the invasion of large SFTPs into adjacent mediastinal and major vascular structures. It is helpful to distinguish the tumor from other structures and to confirm intrathoracic localization in the case of tumor-diaphragm adjacency [18].

Angiography is an important diagnostic tool for demonstrating the invasion of vascular structures. In determining the extrapulmonary origin of SFTPs, it may be useful to demonstrate blood build up from the lower phrenic, intercostal, or internal mammary arteries. Angiography and arterial embolization before surgery may be a good approach to reduce the frequency of bleeding in large SFTP cases [19].

The use of ultrasonography in the diagnosis and evaluation of SFTPs is rare. The combined use of immunohistochemical analysis with ultrasound-guided fine needle biopsy is a safe and quick procedure to provide a preoperative diagnosis [20].

18-fluorodeoxyglucose positron emission tomography (FDG-PET) has been documented as a valuable contribution to the diagnostic tools of SFTPs. It can be used in the diagnosis and follow-up of patients. The presence of multiple SFTPs and high grade 18 FDG metabolism on PET should alert the clinician for a high probability of malignant SFTPs [21].

Preoperative differential diagnosis of SFTPs includes mass lesions ranging from lung cancer to various intrapleural sarcomas. In the case of posterior intrathoracic localization, neurogenic tumors should be considered in the differential diagnosis, whereas thymic neoplasms, germ cell tumor, or teratoma should be considered in anterior and medial regions [22]. Primary differential diagnoses of malignant SFTPs include pleural mesothelioma, neurogenic sarcoma, synovial sarcoma, hemangiopericytoma, fibrosarcoma, and malignant fibrous histiocytoma [23]. Pleural mesotheliomas are malignant and usually present as multiple pleural nodules or as a diffuse tumor covering a portion of the lung.

Treatment

The most significant treatment modality of patients with SFTP is complete surgical excision. Aggressive surgery is recommended due to high recurrence rates [24]. Massive intraoperative bleeding may occur due to tight adhesions to adjacent tissues or vascular structures. Bleeding can be prevented by removal of the mass with a good exploration, tight bleeding control, or preoperative arterial embolization [25]. The type of surgical resection varies based on the size of the tumor, the degree of invasion, and adherence to adjacent structures. Complete en bloc surgical resection is the basic treatment method for all benign and malignant SFTPs.

The normal tissue of 1–2 cm around the tumor should also be resected. Large sessile tumors can sometimes be difficult to resect due

to intense adhesions, whereas pedunculated tumors can be safely resected by lung wedge resection. Pulmonary resection (segmentectomy, lobectomy, bilobectomy, and pneumonectomy), partial pleurectomy, or en bloc chest wall resection may sometimes be necessary for complete resection [26]. Frozen operation during surgery may help in determining surgical tumor margins. Extrapleural dissection may be required in cases adherent to the thorax wall. In case of invasion to the chest wall, simultaneous chest wall resection may be required [27].

Thoracoscopic approaches can be used for the resection of small pedunculated tumors on the visceral pleura. Mostly, the resection of an adjacent small section of the lung and pedunculated lesion may be sufficient. Surgical resection of SFTPs with VATS showed local recurrence and metastases in port regions in some patients [27].

Long-term imaging follow-up is recommended to exclude tumor recurrence or metastasis in all cases. Recurrence may occur even after many years, and the recurrent disease affects the ipsilateral pleura or lung. Resection of recurrent lesions is recommended [28].

The role of adjuvant therapy is questionable due to low cellular content and low mitotic rates of SFTPs. This has not been systematically investigated due to a limited number of patients. Radiotherapy and chemotherapy are considered to be useful in some patients. The application of adjuvant therapy after resection in malignant sessile tumors is recommended especially in recurrent tumors. Although neoadjuvant therapy is useful in large malignant tumors, its use is limited due to difficulty in obtaining a definite preoperative diagnosis even with an open biopsy [29].

Additional therapies such as brachytherapy and photodynamic therapy have been developed for malignant mesotheliomas. These new treatment methods can be applied to other pleural tumors, especially if they are unable to be completely resected. However, their use in SFTPs has rarely been reported, and their benefits have not been proven [30].

Prognosis

Prognosis is generally good for SFTP patients. The majority of lesions behave in a benign manner (88%), but intense intrathoracic tumor growth or unresectable relapse is observed in approximately 12% of patients [5]. Malignant tumors can metastasize and local recurrences are more common in malignant lesions than benign lesions [31]. Recurrence may occur even years after surgical resection and is usually located in the same hemithorax. Intrathoracic recurrence may be fatal due to mediastinal compression and inferior vena cava obstruction. Metastases usually occur through blood. Metastasis most frequently occurs in the liver, central nervous system, spleen, peritoneum, adrenal gland, gastrointestinal tract, kidney, and bone. The risk of recurrence after resection of malignant sessile SFTPs is high. While most of these are initially located within the pleural cavity, distant metastases occur in the later course of the disease. Some recurrences can be highly local aggressive, leading to the death of the patient through local invasion and compression without evidence of distant metastasis. Recurrence mostly occurs within the first 2 years after resection of malignant sessile tumors, and during this period, recurrence is the cause of approximately 50% of mortality. Therefore, it is recommended to perform radiographic controls via chest X-ray or CT once every 6 months during the first 2 years after resection and once a year after 2 years. Aggressive surgical resection is the treatment of choice for recurrent SFTPs and may provide long-term survival [17].

Diffuse Pleural Tumors

The pleura is composed of mesothelium and connective tissue that surrounds the lung (visceral pleura), mediastinum, diaphragm, and chest wall (parietal pleura). Except for observed rare primer malignant tumors of the pleura, most malignant lesions affecting the pleura are diffuse malignant mesotheliomas. Malignant pleural mesothelioma (MPM), which originates from

mesothelial cells lying in the pleura, is a rare, malignant tumor with poor prognosis. There are intense discussions and studies in both diagnosis and treatment.

Etiology and Epidemiology

The important risk factor involved in the etiology of MPM is exposure to asbestos or erionite, which are mineral fibers. The disease develops as a result of the inhalation of these fibers. The cases diagnosed as MPM varies according to series, but exposure to asbestos has been reported in 80% of patients [32].

Asbestos is a natural, fibrous silicate mineral and is divided into two main groups, namely, amphibole and serpentine. Despite controversies, the World Health Organization recognizes that all types of asbestos can cause cancer. Contact with asbestos may be occupational and environmental. In developed countries, the source of contact is mainly occupational. Asbestos is often used in roofing materials, friction-related materials, cement-making materials, and gas masks. Mesothelioma is caused by exposure to erionite, which is the environmental source of fibrous minerals. Erionite fibers have a fibrous structure and are a more powerful carcinogen than asbestos fibers. It is a volcanic product that is naturally found in stone or rock layers [33, 34].

The prevalence of MPM is 1–2.2 million for a year. The reported average annual mesothelioma incidence rate worldwide is 1.3 per 100,000 people per year for men and 0.2 per 100,000 people per year for women [35]. There are more than 15,000 cases around the world, and the number continues to increase significantly [36].

Clinical Features

Environmental asbestos exposure is equally seen in men and women. Mesothelioma due to occupational asbestos exposure is most common between the fifth and sixth decades [37]. The latent period between asbestos exposure and mesothelioma is around 20–40 years. The most common findings are dyspnea and nonpleuritic chest pain, although patients can be asymptomatic [38]. Pain is a common symptom in mesothelioma and is usually seen in the late stages of the disease. Clinical findings are usually associated with disease stage. In the early stages, fatigue, weakness, and weight loss are rare findings. There is a diagnostic problem in early-stage disease because the patient comes with dyspnea caused by massive pleural fluid. Often, the fluid is drained and the patient's complaints improve, but the tumor areas are not radiologically large so it cannot be diagnosed [39]. In anamnesis, asbestos and erionite exposure should be questioned in patients with massive pleural effusions with chest pain. Local complications such as dysphagia, hoarseness, cord compression, brachial plexopathy, Horner's syndrome, or vena cava superior syndrome may occur because of local invasion of thoracic structures [40]. In the terminal period, the effect of shunting in the bloodstream arises due to the increase of tumor spread to the lung. This effect does not respond to oxygen supplementation in the patient, and it may cause hypoxemia and makes shortness of breath more dramatic.

Radiological Findings

A chest X-ray examination can detect strongly a relatively unique radiological finding of MPM in the advanced stages of the disease; however, in the early stages, the sensitivity and specificity of the radiography are low compared with other pleural diseases. Pleural fluids, pleural thickening, the appearance of nodules or masses associated with the pleura, and changes in the pleura attached to adjacent structures are seen [41] (Fig. 3). Pleural fluid is unilateral in 60% of cases and is more local to the right. In 5% of cases, bilateral fluid is seen. Approximately 10% of the patients may not have a pleural fluid image but show pleural thickening or a nodule/mass image. The pleura is seen as a radiopaque line starting from the upper parts of the hemithorax and descending down to the diaphragm [42].

Computed thorax tomography (CTT) is used in the localization of MPM-related pleural

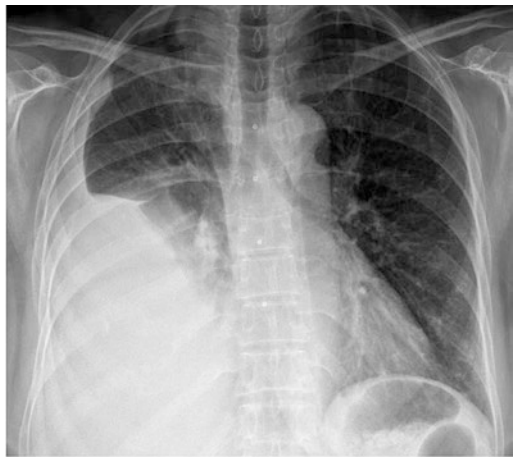

Fig. 3 Chest X-ray pleural thickening fluid

lesions, the degree of spread of the disease, and follow-up of the cases after treatment. Pleural fluid, thickening of the pleura with a smooth or irregular surface, widespread nodular thickening, and pleural-based mass are detected [43] (Fig. 4). Magnetic resonance imaging (MRI) examination is valuable in the demonstration of muscle involvement of the chest wall of the tumor, invasion of the pericardium, and evaluation of the diaphragm and subcutaneous involvement [44]. However, multiplanar CTT may provide similar information to MRI in these areas [45]. In a patient diagnosed with MPM, a contrast agent should be used in the CTT examination if there are no contraindications and should be taken to fill the upper abdomen with thorax together. Ultrasonography should be performed to determine the location of fluid and thickening of the pleura and used as a guide in pleural needle biopsies.

Fluorodeoxyglucose positron emission tomography (FDG-PET)/CT imaging is used for diagnostic purposes in the presence of recurrent pleural effusion and/or pleural thickening. If the tumor load is not high in patients with MPM or the pleural thickening or pleural lesions are less than 1 cm, PET may be negative. It cannot clearly do MPM distinction with other pleural malignancies. Standard oncologic FDG-PET/CT imaging is performed for pretreatment staging in patients with a histopathological diagnosis of MPM. PET/CT is a more appropriate method for the evaluation of distant metastasis and mediastinal lymph node [46].

Diagnosis

Since approximately 90% of the patients were admitted with pleural fluid, thoracentesis is applied as the first method, which is the

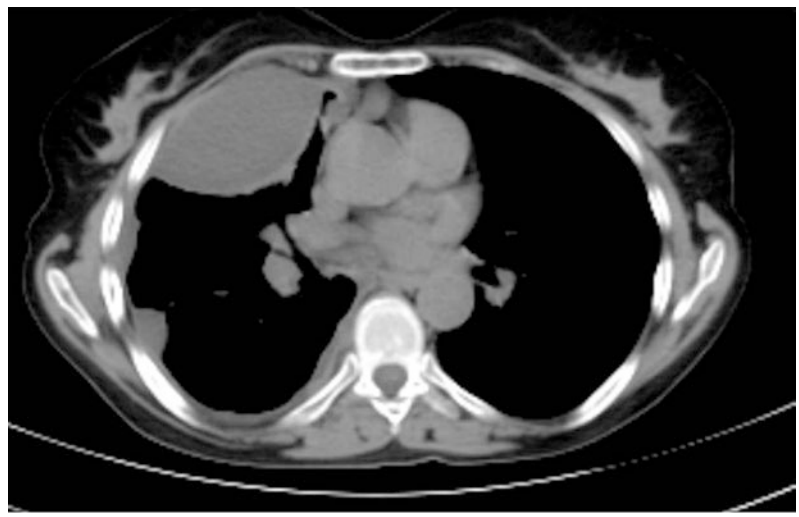

Fig. 4 Computed thorax tomography pleural thickening fluid in the right hemithorax

diagnostic method for a cytological examination. Pleural fluid is generally exudate and approximately hemorrhagic in about half of the cases. Lymphocyte count, protein amount, and LDH are high in the fluid. Atypical mesothelial cells are observed in aggregates [47].

A pleural needle biopsy is a tissue sampling for histopathological examination of the parietal pleura with the help of a special needle. This procedure is performed by a ultrasonography or CT-guided Trucut needle. The most important advantages are low complication rate, no hospitalization, ease of repetition, and economic. However, the small sample size and the blindness of the procedure are the most important disadvantages [48, 49].

Video-assisted thoracoscopic surgery (VATS) is a highly effective and reliable method for the diagnosis and treatment of pleural diseases. It provides sufficient size and multiple tissue samples by seeing from pleural lesions. The success of VATS in the diagnosis of pleural pathologies is over 90%. The characteristic of the macroscopic appearance of the pathological structure for MPM is reported to occur showing the trend of merger, gray-light yellow-white color, and bright nodules of varying sizes, but it is not diagnostic. In metastatic tumors especially adenocarcinoma, metastasis may also give this type of image [50]. As a result of improvements in VATS, a diagnostic thoracotomy is used in rare cases such as patients who cannot be diagnosed by other methods and patients who can be diagnosed and treated in the same session [47].

Staging

MPM is a neoplasm with a high mortality rate due to the serosal surfaces of the pleural cavity. Accurate staging is very important for treatment and prognosis. Although many staging systems have been proposed to date, studies continue to be intense since they are not adequate to their prognosis. The most widely used staging system for MPM was discussed in 1994 at a workshop sponsored by the International Mesothelioma Interest Group (IMIG) and the International Association for the Study of Lung Cancer (IASLC) called the tumor-node-metastasis (TNM) staging system. TNM has been updated with the IASLC mesothelioma staging project. The common clinical variables with prognostic effect and TNM parameters were examined. Because there was no clinical and pathological information for all patients, the data were combined to obtain the best TNM. The separation of T1a and T1b available in the IMIG staging system has been removed. It has been suggested that measurement of tumor thickness may be useful instead. As a result of the multicenter analysis of 2,432 cases related to the N classification, it was decided that N1 and N2 should be combined. Any ipsilateral intrathoracic lymph node (LN) is reclassified as N1 and the old N3 as N2. In the IASLC mesothelioma staging project, the proposal for N is given. This is a relationship between the maximal thickness and LN positivity. However, more extensive studies are needed. As a result, it was concluded that LN metastasis is an important factor in survival and that the N1 and N2 classifications are not suitable for anatomic MPM. In the IASLC mesothelioma staging project, there is no difference in survival between a single and multiple lesion or localization; therefore, all metastases should be considered as M1 [51–54] (Table 1).

Surgical Treatment

The aim of surgical treatment is to resect the tumor tissue as much as possible, to eliminate or reduce the patient's symptoms. Multiple factors such as the stage of the disease, cardiopulmonary reserve, surgical experience, and scope of the planned adjuvant therapy determine the choice of surgical technique [55]. There are two types of surgical method: extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D).

Extrapleural Pneumonectomy

EPP is the removal of the lung, pleura, diaphragm, and pericardium in a hemithorax. EPP may be the best treatment modality in early-stage MPM patients with epithelioid histology

Table 1 Staging; Eighth edition of the TNM classification for malignant pleural mesothelioma

T—primary tumour	
T1	Tumour involving the ipsilateral parietal or visceral pleura only
T2	Tumour involving ipsilateral pleura (parietal or visceral pleura) with invasion involving at least one of the following: • diaphragmatic muscle • pulmonary parenchyma
T3	Tumour involving ipsilateral pleura (parietal or visceral pleura) with invasion involving at least one of the following: • endothoracic fascia • mediastinal fat • chest wall, with or without associated rib destruction (solitary, resectable) • pericardium (non-transmural invasion)
T4	Tumour involving ipsilateral pleura (parietal or visceral pleura) with invasion involving at least one of the following: • chest wall, with or without associated rib destruction (diffuse or multifocal, unresectable) • peritoneum (via direct transdiaphragmatic extension) • contralateral pleura • mediastinal organs (oesophagus, trachea, heart, great vessels) • vertebra, neuroforamen, spinal cord or brachial plexus • pericardium (transmural invasion with or without a pericardial effusion)
N—regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases to ipsilateral intrathoracic lymph nodes (includes ipsilateral bronchopulmonary, hilar, subcarinal, paratracheal, aortopulmonary, paraoesophageal, peridiaphragmatic, pericardial, intercostal and internal mammary nodes)
N2	Metastases to contralateral intrathoracic lymph nodes. Metastases to ipsilateral or contralateral supraclavicular lymph nodes
M—distant metastasis	
M0	No distant metastasis
M1	Distant metastasis present

Stage	**T**	**N**	**M**
IA	T1	N0	M0
IB	T2, T3	N0	M0
II	T1, T2	N1	M0
IIIA	T3	N1	M0
IIIB	T1, T2, T3	N2	M0
	T4	N0, N1, N2	M0
IV	Any T	Any N	M1

and pleura-limited, mediastinal LN non-involvement. Radiologically, the disease should be limited to the hemithorax and should have no transdiaphragmatic, transpericardial, and diffuse chest wall invasion [56].

Pulmonary evaluation should be performed with caution because the hemidiaphragm is removed, and this affects the operation of other hemidiaphragm and disturbs the respiratory dynamics. In the pulmonary function test,

FEV1 should be calculated according to ventilation-perfusion scintigraphy and at least 1 L after pneumonectomy [57]. Patients should be evaluated in terms of cardiac function after pneumonectomy and accompanying pericardial resection. Routine cardiac evaluation, in addition to electrocardiography and echocardiography, is recommended. In case of a history of the disease, exercise stress test and, if necessary, thallium cardiac scintigraphy or angiography should be carried out. Echocardiography is performed to evaluate ejection fractions, pericardial effusion, and myocardial invasion. In echocardiography, left and right ejection fractions should be at least 45%, and tricuspid failure should not be present [57].

EPP is one of the major thoracic surgeries. In order for the surgery to be technically perfect, the steps must be done in a regular and orderly manner, and surgical technique directly affects morbidity and mortality. A double-lumen tube and nasogastric tube are inserted in the patient. The central vasculature is placed through the internal jugular or subclavian vein. Except for the central vascular tract, the opening of one or two other vessels is necessary for adequate fluid replacement during surgery.

Posterolateral thoracotomy is performed to the patient in a lateral decubitus position. A long S-shaped incision is made from the anterior axillary line to the posterior of the scapula. After passing the skin and subcutaneous tissue, the latissimus dorsi muscle is completely cut, and then, the serratus anterior muscle is preserved and the costal cartilage is reached. The sixth cage is released as subperiosteal and cut with the jeans cutter. Some authors performed a second thoracotomy for the convenience of the diaphragm resection. The first thoracotomy is from the intercostal space, while the second thoracotomy is from the eighth intercostal space [58].

Extrapleural dissection, which is performed to remove the tumor from the chest wall, should be done between the endothoracic fault and the pleura. If there is diffuse chest wall, transdiaphragmatic or mediastinal invasions are detected during surgery and the operation should be terminated (Fig. 5). In cases where the tumor overcomes the endothoracic fascia and invades the chest wall, a local invasion wall resection can be performed. Dissection of the superior vena cava and internal mammary artery should be carried out carefully in the right EPP. In the left EPP, the aim should be to invade the subclavian artery by a tumor. Diaphragm resection is the next stage after extrapleural dissection. Extrapleural dissection should be performed on the costal face of the diaphragm, in the paravertebral sulcus, until it reaches the muscle tissue. The diaphragm is first cut from the lateral edge and then from the anterior to the posterior. If not invaded, the lower part of the diaphragm is released with the peritoneum. Diaphragm resection is performed in the anteromedial of the pericardium. Then, diaphragmatic fibers are released to the lateral and posterior areas. Diaphragm resection should be performed very carefully, and sufficient diaphragm tissue should be left around the inferior vena cava on the right and the esophageal hiatus on the left.

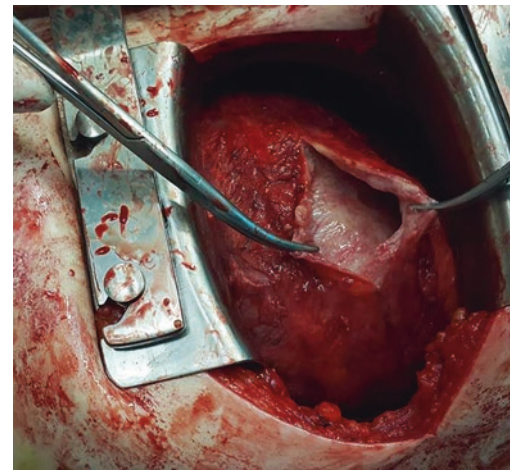

Fig. 5 Extrapleural dissection, remove the tumor from the chest wall

Pericardial resection is started from the anterior region of both sides of the pericardium. The anterior incision is extended superiorly and inferiorly, and the pericardium is cut together with the diaphragm. It is recommended to leave the pericardium edge at the posterior part to prevent the esophagus from contacting the mesh. Right-side pericardial resection of the inferior and

superior vena pericardial edges should be left to secure the mesh on the vena cava. If right lung resection is performed intrapericardially and firstly in the inferior pulmonary vein, then the superior pulmonary vein and the last right main pulmonary artery are cut. In the left lung, the veins are cut intrapericardially, and the left main pulmonary artery is cut as extrapericardial. After hilar veins are cut, the incision is applied to the posterior pericardium, and the pericardial resection is completed. The bronchus is dissected and cut. For proper staging, LN dissection should be performed. With the discontinuation of the bronchus, the en bloc resection of the lung, pleura, pericardium, and diaphragm is completed, and the specimen is removed from the thorax.

The material to be used for diaphragm reconstruction should not be absorbed and should be sufficiently strong and flexible enough to compensate for intraabdominal pressure increases. Sugarbaker and his team used a 2-mm thick polytetrafluoroethylene (PTFE) patch for diaphragm reconstruction [57]. In recent years, two pieces of 2-mm thick Gore-Tex grafts (20×30 cm) are used to be reconstructed at the center with a slight overlap on each other in order to better compensate the pressure increases of the artificial diaphragm. The advantage of this type of patch is that it can be easily seen during tomography and provides ease during radiotherapy planning. Diaphragmatic patch is sutured anteriorly, laterally, and posteriorly to the chest wall. The suture passes through the patch and the intercostal space. The space in the pericardium is larger on the left side and smaller on the right side. The most important criterion in the choice of a patch in pericardial reconstruction is to minimize cardiac irritation and not to cause tamponade. As the PTFE patch can be used, the absorbable patch is also used. The patch is sutured to the edge of the pericardium and the diaphragmatic knee medially.

Pleurectomy/decortication

Pleurectomy is the separation of the pleura from the chest wall and removal of the pleura. The aim of pleurectomy is to remove the surrounding tissue of the lung and pleura, provide easier breathing, and reduce the likelihood of fluid accumulation in the pleural space. Decortication forms the second part of the operation. The aim is to remove the tissue on the lung by peeling off and expanding the lung. Indications for a P/D operation vary depending on the surgeon or tumor. While there is no case of patients who cannot tolerate a pneumonectomy operation, the necessity of EPP is controversial when there is no lung involvement in patients with adequate cardiopulmonary reserves. The removal of diaphragm and pericardium with P/D is called Radical P/D.

Taioli et al. conducted a meta-analysis of 1,512 patients who underwent P/D and compared them with 1,391 patients who underwent EPP. The study found that early mortality was higher in the P/D group (4.5%) than in the EPP group (1.7%). In addition, the median survival was high in patients who underwent EPP at 53%. There was no statistically significant difference between the two groups in the 2-year mortality (23.8% vs. 25%) [59].

Multimodal Treatment

Multimodal treatment consists of surgery, radiotherapy, and chemotherapy. The aim is to remove the tumor macroscopically with radical surgery, provide local control with radiotherapy, and reduce the frequency of distant metastases by chemotherapy or destroy micrometastases [60]. There are three main methods in multimodal therapy:

1. Consecutive radiotherapy and chemotherapy for adjuvant purposes after EPP: radiotherapy is administered at different doses and all hemithorax. Chemotherapy is usually a pemetrexed-cisplatin combination [61].
2. EPP and radiotherapy after neoadjuvant chemotherapy: after pemetrexed-cisplatin treatment, EPP is applied and radiotherapy is started 1 month following surgery. The low rates of response to chemotherapy in MPM cause some patients to be programmed during treatment [62].

3. Adjuvant chemotherapy after radical pleurectomy: total pleurectomy with diaphragm and pericardial resection is performed and all visible tumoral lesions are resected. Then, adjuvant chemotherapy is applied [63].

The prognosis of MPM is generally poor. Life expectancy in a large case series is between 6 and 17 months, while median survival is 12 months or less [64]. The median survival after multimodality treatment ranged from 19 to 26 months [60–67]. Surgical treatment with additional chemotherapy/radiotherapy for early stage, epithelial type, and the absence of LN involvement are factors that affect survival. Non-epithelial cell type and right-sided tumor were associated with poor prognosis in patients receiving multimodal therapy [68].

Conclusion

Primary pleural tumors are very rare. 90% of these tumors are mesothelioma, 5% are solitary fibrous tumors and 5% are other tumors. The most important treatment for pleural tumor complete en-bloc resection although it depends on the size of the tumor and its relation to the surrounding structures. The prognosis should be evaluated with clinical biological and imaging factors of the patient. Patients should be follow up for a long time in the postoperative period because of the possibility of recurrence.

Self-study

1. Which statement/statements is/are true?
   a. SFTP is more commonly caused by parietal pleura than by visceral pleura.
   b. Long-term imaging follow-up is recommended after en block resection.
   c. SFTPs are always benign
   d. Preoperative arterial embolization can be performed.
2. Which statement/statements is/are true?
   a. The most common tumor of the pleura is a solitary fibrous tumor.
   b. Malignant pleural mesothelioma may develop as a result of inhalation of asbestos dust so important occupational and environmental investigation is important.
   c. PET-CT is used in the localization of MPM-related pleural lesions, the degree of spread of the disease, and follow-up of the cases after treatment.
   d. Multimodal treatment consists of postoperative radiotherapy and chemotherapy.

Answer

1. Which statement/statements is/are true?
   a. Approximately 80% of SFTPs are originated by the parietal pleura, whereas 20% originate from the visceral pleura.
   b. CORRECT. Long-term imaging follow-up is recommended to exclude tumor recurrence or metastasis in all cases. Recurrence may occur even after many years.
   c. They can also be malignant. The criteria for malignancy are high mitotic activity, nuclear pleomorphism, increased cellularity where nuclei are intermixed, the presence of necrotic or hemorrhagic areas, and stromal or vascular invasion.
   d. CORRECT. Massive intraoperative bleeding may occur due to tight adhesions to adjacent tissues or vascular structures. Bleeding can be prevented by removal of the mass with preoperative arterial embolization.
2. Which statement/statements is/are true?
   a. Primary pleural tumors are very rare. 90% of these tumors are mesothelioma, 5% are solitary fibrous tumors and 5% are other tumors.
   b. CORRECT. The cases diagnosed as MPM which exposure to asbestos has been reported in 80% of patients. Contact with asbestos may be occupational and environmental. In developed

countries, the source of contact is mainly occupational. Asbestos is often used in roofing materials, friction-related materials, cement-making materials, and gas masks.

c. FDG-PET/CT imaging is performed for pretreatment staging in patients with a histopathological diagnosis of MPM. PET/CT is a more appropriate method for the evaluation of distant metastasis and mediastinal lymph node.

d. CORRECT. Radical surgery provides to macroscopically remove tumor, provide local control with radiotherapy, and reduce the frequency of distant metastases by chemotherapy.

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Intraoperative Accidents and Postoperative Complications in the Surgery of Pleural Tumours

Mustafa Vayvada, Erdal Taşçı, and Ali Yeğinsu

Glossary

Complication An unfavorable evolution or consequence of a disease a health condition or a therapy.

Morbidity Having a disease or a symptom of disease or to the amount of disease within a population. Morbidity also refers to medicalproblems caused by a treatment.

Mortality The state of being mortal (destined to die). Inmedicine a term also used for death rate or the number of deaths in a certain group of people in a certain period of time.

Pleural empyema Precence of pus in pleural cavity.

Chylothorax An effusion of chyle or chylous fluid into the thoracic cavity.

Hemothorax Blood in the pleural cavity.

Herniation Abnormal protrusion of tissue through an opening.

Epicarditis Inflammation of the epicardium (outer lining of the heart).

Sepsis The presence of bacteria (bacteremia) other infectious organisms or toxins created by infectious organisms in the bloodstream with spread throughout the body.

Key Points

1. Pleuralectomy/decortication and extrapleural pneumonectomy are two main surgical procedures for the treatment of pleural tumors. Postoperative complications are quite diverse and their incidence is high. The incidence of complications in P/D is higher than EPP (46% vs. 24%).
2. In the management of complications preoperative full evaluation of the patients and the precautions and prophylaxis should be made completely the surgery should be done by meticulous and experienced hands and early diagnosis and agressive approach should be performed.
3. Specific complications associated with the use of pericardial and diaphragmatic patch in EPP (tamponade cardiac herniation diaphragmatic herniation) and bleeding require urgent surgical intervention. In the treatment of intrathoracic infectious complications the removal of the patch is the key step.
4. Stabilization of mediastinum is important after EPP. In case of cardiac arrest the mediastinal stabilization should be completed in order to have an effectual external cardiac massage. And also in empyema the mediastinum should be stabilized before removal of infected patches.

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Introduction

Generally, pleurectomy/decortication (P/D) and extrapleural pneumonectomy (EPP) are the most commonly used surgical procedures in malignant pleural mesothelioma (MPM). MPM surgery is a cytoreductive surgery, and even in EPP with maximal tissue removal, microscopic surgical margin positivity is reported to be 70–100% [1, 2]. MPM is a highly aggressive tumor and median survival despite trimodal treatment is 12–22 months in EPP, 9–32 months in PD and 7–14 months in palliative pleurectomy [3, 4].

Although complications of EPP and P/D are frequent, they have an acceptable mortality rate. In EPP, major and minor morbidity increases between 12.5 and 60.4% [4, 5]. While initial mortality rate was 31% [6], subsequent rates decreased to 6–13% [7], and finally the mortality rates decreased below 5% in experienced centers [8].

In this section, the complications after EPP and P/D, and the management of these complications will be explained.

Table 1 Intraoperative accidents and postoperative complications after EPP for MPM

Operative site complications	Systemic complications
Technical issues Bleeding Patch problems Tamponade Cardiac herniation Diaphragmatic herniation	Cardiac complications Atrial fibrillation Myocardial infarctus Cardiac arrest Cardiac failure Epicarditis
Nerve injuries, Recurrent laryngeal nerve Phrenic nerve Vagal nerve	Pulmonary complications Prolonged entubation Aspiration ARDS Tracheostomi Atelectasis Pneumonia Pulmonary embolus
Empyema Bronchopleural fistula Hemothorax Chylothorax, Oesophago-pleural fistula Wound complications	Other system complications Renal failure Deep venous thrombosis Cerebrovascular event Ischemic colitis Ileus Sepsis

Intraoperative Accidents and Postoperative Complications

Complications developing after EPP and P/D can be classified as operative site complications and systemic complications. Operative site complications are technical issues [bleeding and patch problems], empyema, hemothorax, chylothorax, bronchopleural fistula, nerve injuries and systemic complications are cardiac, pulmonary and other system complications. A detailed complication list is given in Table 1.

Operative Site Complications

Technical Issues

Bleeding: Bleeding is common in EPP and P/D. The bleeding site is often the bronchial artery or systemic arteries in the chest wall. Bleeding due to coagulation disorders is rare. Inadequate hemostasis is the main cause. The frequency of major bleeding requiring revision is about 4–8% [9, 10]. In 47% of patients who underwent EPP, 33.7% of patients who underwent P/D need an intraoperative blood transfusion [8]. The risk of hemothorax is high after EPP due to the absence of a tissue that will tamponade the small veins feeding the pleura in the chest wall after pneumonectomy. Yan et al. [13] reported the incidence of hemothorax as 10%. Intraoperative bleeding control should be performed meticulously. Hemorrhages developing after chest tube removal may cause mediastinal shifting. Postoperative bleeding should be emergently reoperated and controlled.

- Do meticulous bleeding control intraoperatively.
- Reopen the thorax and stop hemorrhage if there is a postoperative bleeding.

Patch problems: The patch placed on the pericardium or diaphragm may be too tight or loose, and the patch may be separated from the stitched tissue. Excessively tight or loose or inadequately fenestrated pericardial patch may causes cardiac tamponade. Excessively tight patch compresses the inferior of the vena cava and impair the venous return. The incidence of tamponade was reported as 3.6% [5]. Dehiscence of the pericardial patch or excessive fenestration in the patch may cause cardiac herniation (0.3–1.5%) [5, 14, 15]. In both cases, patch problem should be eliminated with emergent surgical intervention.

In the diaphragm, excessively loose patch may cause the diaphragm elevation, causing intrathoracic restriction and atelectasis. When the patient is in supine position, the upward movement of the liver compresses the heart, causing venous return impairment. When the patient is placed in the supine position, evidence of the symptoms should be coutionary. Transesophageal echocardiography is useful in early diagnosis [5]. Excessively tight patch can cause tension and tears at tissues. In the diaphragm, patch dehiscence is seen in 5–13% [9, 11, 16, 17] and is common in the weakest site which is at the esophageal hiatus area. Diagnosis can be made by imaging methods. Diaphragmatic herniation should emergently be repaired surgically.

- Do not place the patches too tight or too loose.
- Keep in mind the probability of tamponade and herniation if you used patch in MPM surgery

Nerve injuries: Mechanical or thermal damage of the intrathoracic nerves may occur during dissection of the mediastinal region. Laryngeal nerve damage was reported as 2.1–11% [5, 10, 18–21]. Depending on the vocal cord paralysis, hoarseness, weakness in cough, aspiration and consequently pneumonia may develop. It is a life-threatening condition especially in patients with pneumonectomy. Vocal cord medialization with gelfoam injection has been reported to give good results [5]. Bille et al. [10] reported that Horner's syndrome developed in 1(4%) patient. Although theoretically, phrenic and vagal nerve injuries are possible, sufficient information could not be obtained in the literature.

- Diagnose and threat vocal cord paralysis early especially in patients underwent EPP.

Pleural empyema: Incidence is between 2.4 and 15.8% [5, 9, 22]. The presence of a prosthetic patch makes the treatment of empyema difficult and the result can be fatal. For infection prophylaxis, thoracic cavity irrigation, wide spectrum multi-antibiotics and drainage of the thorax with a small calibre drain is recommended [5].

The management of empyema varies depending on the time and the presence of bronchopleural fistula (BPF). In the early period and if there is no BPF, debridement, irrigation and removal of the patches after stabilization of the mediastinum may be sufficient in the treatment. The procedure can be thoracoscopic or open.

In the presence of gross pus and/or BPF, an open drainage should be performed with Clagett procedure and patches should be removed after 2–3 weeks of mediastinal stabilization. The rate of development of BPF after EPP is 2.7–12% and is more common after right pneumonectomy. It is frequently associated with prolonged mechanical ventilation [23]. Open drainage and removal of patches is essential for effective treatment [5, 9, 10, 22, 24]. After sterilization of the thoracic cavity, empyema is treated with primary thoracic closure or thoracoplastic interventions.

- Removing the infected patches after mediastinal stabilization is crucial in the management of pleural empyema.
- Do open drainage for pleural cleaning if BPF present.

Esophagopleural fistula: Esophagopleural fistula is a rare complication. The incidence was reported to be 1–2% [15, 19, 25]. It may occur due to mechanical or thermal damage, tumor recurrence or chronic infection. In trimodal therapy, some cases developing after radiation exposure have been reported [26]. Early diagnosis and treatment is vital. If it is not treated properly, it is fatal due to the development of mediastinitis and sepsis.

Chylothorax: Although chylothorax is considered to be rare, its prevalence is reported to be 1–14.3% in several publications [9, 24, 27–29]. It usually occurs during dissection of the paravertebral inferior right hemitorax in EPP [30]. It may cause rapid fluid accumulation and mediastinal shifting in the thoracic cavity. Diagnosis is made by thoracentesis. In the management, withdrawal of oral feeding, total parenteral nutrition, somatostatin analogues, percutaneous embolization of the thoracic duct, or surgical ductus ligation can be performed.

Prolonged air leak: Prolonged air leak after P/D (>5 days) is seen in 9.8–58% of patients [18, 31, 32]. Prolonged air leak increases the length of hospital stay and cost of treatment but does not directly affect morbidity and mortality.

Systemic Complications

Cardiac Complications

Atrial fibrilasyon Atrial fibrillation is the most common complication. The incidence is between 8.4 and 44.2% in different sources [5, 10, 13, 18–21, 33]. Sugarbaker et al. [5] reported that large pericardial resection was a predisposing factor in atrial fibrillation. Some other risk factors; advanced age, removed lung volume, increased serum BNP level, underlying heart disease, electrolyte imbalance [34].

Atrial fibrillation is associated with thromboembolic events, hemodynamic deterioration, increased morbidity and mortality [34]. To date, no proven success has been achieved in any of the strategies that have been tried for preoperative and postoperative prophylaxis [5]. Some centers currently use beta-blockers or calcium channel blockers for postoperative prophylaxis. Antiarrhythmic drugs, cardioversion or catheter ablation speed control is provided. Anticoagulation therapy should be given if AF continues over 48 hours.

Myocardial infarction is not common. The incidence is reported as 1.5% and is among the causes of death [5]. However, pericarditis is more common in patients after EPP characterized by ST segment elevation and elevation in cardiac enzymes. ECG findings and enzyme levels usually return to normal within 48 hours.

In patients who develop cardiac arrest within the first 10 days after EPP, external cardiac massage may fail because the mediastinum is not stable. In such a case, internal cardiac massage should be performed with emergency thoracotomy and the underlying pathology should be corrected.

- Keep in mind that external cardiac resuscitation may fail in early postoperative cardiac arrest after EPP.
- Then, do rethoracotomy urgently and do open cardiac massage.

Acute right heart failure is due to pulmonary hypertension caused by the decrease in the vascular bed of the lung after EPP. Hypoxia, hypercarbia and acidosis increase the severity of pulmonary hypertension. Early diagnosis and treatment is necessary. Deadly results occur when untreated. It may be fatal when untreated. In patients undergoing EPP, preoperative echocardiography and right heart catheterization should be performed to evaluate pulmonary hypertension. The patients had hypotension, peripheral edema, end-organ hypoperfusion, and high central venous pressure. Elimination of predisposing factors, fluid restriction and diuresis, inotropes, pulmonary vasodilator agents are used in the treatment.

Epicarditis and constructive cardiac physiology may develop in 2.7 of patients after EPP [5]. It is due to epicarditis and a fibrous layer covering the surface of the heart. It can be detected by echocardiography or cardiac catheter. Byrne et al. [35] reported constructive cardiac physiology in 7 patients who underwent left EPP without pericardial reconstruction. In these patients, the problem was resolved by reoperations and epicardiectomy.

Pulmonary Complications

Atelectasis: Atelectasis may occur after EPP and P/D due to secretion accumulation, aspiration, bronchospasm, decreased lung compliance, pain-induced hypoventilation and inability in coughing, mediastinal shifting and restriction. Burt et al. [18] reported that atelectasis requiring bronchoscopy occured in 1.7% of patients. The development of atelectasis can lead to respiratory failure, especially in patients with restricted respiratory reserve. The risk of infection develops in the untreated atelectatic lung section. It also causes the formation of pleural space. Atelectasis should be treated with early extubation, mobilization, expectoration, pain control, humidified oxygen and bronchodilators and bronchoscopy. If present, vocal cord paralysis, which disturbs the physiology of cough, should be treated.

Pneumonia: Causes such as prolonged secretions and prolonged mechanical ventilation are often lead to pneumonia. Often, the aspiration of gastric secretions or the bacterial colonization of the atelectatic site is the main cause. After MPM surgery, pneumonia occurs at 3.5–21.4% [9, 10, 18, 27, 36]. Precautionary measures should be taken to prevent secretion accumulation and atelectasis. In addition to the administration of antibiotherapy, humidified oxygen, bronchodilators, expectorants, oxygen support, non invasive mechanical ventilation or mechanical ventilation should be provided if needed.

Pulmonary edema: Pulmonary edema after pneumonectomy is a life-threatening complication. It usually occurs after excessive fluid loading. Heart failure, arrhythmias, septic capillary leak, hypoproteinemia, prolonged high concentration of oxygen ventilation and excessive operative dissection can lead to pulmonary edema. Appearance and symptoms similar with ARDS. Treatment includes diuresis, respiratory support, and elimination of underlying causes.

Adult Respiratory Distress Syndrome (***ARDS***): ARDS is characterized by an acute refractory hypoxemia, diffuse infiltrates on chest X-ray, and severe respiratory failure a pulmonary capillary wedge pressure lower than 18 [37]. The incidence of ARDS after MPM surgery was reported to be 1.6–5% [5, 8, 10, 28, 38]. The risk of mortality in ARDS after pneumonectomy has been reported as 50–100% [39]. Risk factors are showed in Table 2. There is no specific treatment, respiratory support and ECMO, fluid restriction, low-dose steroids, infection therapy and other supportive treatments are the basis of management.

Other System Complications

Acute Kidney Injury (***AKI***): The incidence of severe renal failure after MPM surgery is 2–10% [5, 16, 21, 40]. Renal failure increases the risk of mortality. In the long-term, 9.8% of patients developed sustained damage and increased risk of sustained kidney injury in patients with increase in serum creatinine level more than 58% [40]. In general, the cause of the damage is decreased renal perfusion and tissue ischemia. Toxic drugs can increase the degree of damage. Maintaining hemodynamics and oxygenation

Table 2 Risk factors in ARDS

Preoperative
Age >60 years
Male
Chronic alcohol
Current tobacco abuse
Chronic suppurative disease
Concurrent cardiac disease
Prior radiation or chemotherapy
Intraoperative
Pneumonectomy
High intraoperative ventilation pressures
Intraoperative fluid intake
Extent of tissue resection
Duration of operation
Increased blood loss
Postoperative
Perioperative fluid intake
Nonbalanced drainage of hemithorax with pneumonectomy

stable intraoperative and postoperative period and avoiding the drugs that may be toxic to the kidney is critical in preventing renal damage. Diuretics, hemofiltration or hemodialysis should not be avoided for providing diuresis in patients with advanced damage. Adequate tissue oxygenation, elimination of septic, inflammatory and/or toxic status and nutritional support are the key factors in management.

Thromboembolism: The risk of development thromboembolism after MPM surgery is high and may have fatal consequences after EPP. The risk of developing deep venous thrombosis (DVT) is reported as 0.8–28.6% [5, 27, 41, 42]. Pulmonary embolism occurs in 1.5–4% of patients [5, 9, 18]. Although DVT alone does not carry an important risk of mortality, it also has a great mortality risk when it causes pulmonary embolism, especially after EPP. It is the most common cause of mortality after EPP (30%) [5, 9]. Routine non-invasive studies should be performed before surgery. Vena cava filter can be placed in appropriate patients before surgery. In the presence of clinical suspicion in the postoperative period, every effort should be made to diagnose and post-diagnostic approach should be aggressive.

Sepsis: The incidence of sepsis after MPM surgery was reported as 1.2–6.2% [18, 19]. In general, pneumonia, empyema, esophageal leak and mediastinitis are the causes of sepsis. Burt et al. [18] showed that the rate of sepsis development in low-volume centers was significantly higher than the high-volume centers. Mortality risk is high after sepsis development. Multiorgan failure is the leading cause of death. Early diagnosis, antibiotic therapy, fluid replacement and battle against organ failure are the basis of successful management [43].

Outcomes of EPP and P/D

In the surgical treatment of MPM, EPP and P/D were compared in many studies. Logically, EPP is a much more radical surgical method, so the incidence of morbidity and mortality is expected to be higher than that of P/D. Indeed, Van Gewen et al. [8] found that the prevalence of mortality and morbidity in EPP was 5% and 46% and in P/D 2% and 24%, respectively. In addition, the incidence of arrhythmias was significantly higher in EPP [20% vs. 5%]. It was reported in some other sources that, mortality in EPP is 2.7–8.5% [5, 16, 19, 44, 45] and morbidity is between 12.5–60.4% [5, 46] and mortality in P/D is 0–9.1% [31, 33, 44, 47–49] and morbidity rates of 4–30% [33, 47–50].

Median survival was reported as 14–32 months in P/D [12, 32, 33, 47, 48] and 12–23 months in EPP [13, 19, 20, 32, 33, 44, 51]. No statistical difference was found in several studies. The results show that P/D is less invasive, has less morbidity and mortality and does not show a significant difference with EPP in terms of median survival.

Conclusions/Summary

Surgical treatment of MPM is a challenging process. There is a high risk of developing complications after surgery. However, the mortality rate is acceptable at experienced centers. Minimizing the risk of complications depends on good evaluation of the pre-operative period, performing the surgical procedure in rigorous and experienced hands, taking precautionary measures against preoperative and postoperative risks and good postoperative care. Early diagnosis and rapid and aggressive approach to life-threatening complications is critical for a successful management.

Self-study

1. Which statement is true:
   a. Cardiac herniation is the most common complication after EPP.
   b. Cardiac arrest immediately after EPP requires emergency thoracotomy and internal cardiac massage.
   c. The most common cause of death in EPP is arrhythmia.

   d. The pericardial patch should not be removed in the empyema after EPP.
2. Which statement is wrong:
   a. Major hemothorax should be managed conservatively.
   b. Excessively tight pericardial patch compresses the inferior of the vena cava and impair the venous return.
   c. Chylothorax may cause rapid fluid accumulation and mediastinal shifting in the thoracic cavity.
   d. Constructive cardiac physiology may develop after EPP due to epicarditis and a fibrous layer covering the surface of the heart.

Answers

1. a. Most common cardiac complication is arrhytmia after EPP.
   b. Cardiac arrest immediately after EPP requires emergency thoracotomy and internal cardiac massage. *CORRECT*
   c. Most common cause of death in EPP is pulmonary thromboembolus.
   d. Infected patches should be removed in the empyema after EPP.
2. a. Major hemothorax should be managed surgically. *CORRECT*

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Surgical Anatomy of the Mediastinum

Anna Le Wen Tam and Atasha Asmat

Key Points

1. Clear understanding of the mediastinal compartments allows the thoracic surgeon to establish a differential diagnosis of mediastinal masses based on their location and select the best approach for diagnosis and treatment of mediastinal tumours.
2. Knowledge of thymic anatomy and ectopic thymic tissue is important for the surgical management of myasthenia gravis and thymic tumours.
3. An understanding of the anatomy of mediastinal nerves is important for the evaluation and surgical treatment of thoracic tumours.

Introduction

The mediastinum is the central compartment of the thoracic cavity, situated between the right and left pulmonary cavities and is bordered superiorly by the thoracic inlet and inferiorly by the diaphragm. It is a mobile region, and contains all the thoracic viscera, vessels and structures.

Classifications

As there are no fascial or anatomic planes, several classifications for subdividing the mediastinum have been proposed by anatomists and surgeons. These classifications divide the mediastinum into specific compartments, which has been useful in the identification, characterization and management of various mediastinal abnormalities.

The anatomical classification divides the mediastinum into a superior and inferior mediastinum by an imaginary transverse plane extending from the sternal angle (Angle of Louis) anteriorly to the inferior border of the T4 vertebra posteriorly. The inferior mediastinum is further subdivided by the heart and pericardium into three parts: anterior, middle and posterior.

The most commonly used classification in clinical practice by surgeons is the Shields classification system which divides the mediastinum into 3 zones: anterior, visceral and paravertebral sulci bilaterally [1]. The anterior compartment extends from the undersurface of the sternum and is bordered posteriorly by the anterior surfaces of the great vessels and pericardium. The visceral compartment begins at the posterior

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Table 1 Three mediastinal compartment and contents [2]

Compartment	Organs	Vessels	Nerves
Anterior	Thymus	Internal mammary vessels	
Visceral	Heart and pericardium; Trachea and proximal bronchi; Esophagus	The aortic arch and its branches, ascending aorta; The Superior vena cava, proximal azygos vein, brachiocephalic vein, pulmonary and pericardiacophrenic veins; and the thoracic duct	Phrenic and Vagus nerves
Paraventral sulci		Intercostal arteries and veins; distal azygos vein	Intercostal nerves, thoracic spinal ganglions, and the sympathetic trunk

limit of the anterior compartment and extends to the ventral surface of the vertebral column and occupies the entire space anterior to the spine at the thoracic inlet. The paravertebral sulci are potential spaces that run along the vertebral column and adjacent proximal ribs on each side. Table 1 summarizes the structures found in each region of the mediastinum. Note that some structures pass vertically through the mediastinum and hence are present in more than one compartment.

The Thymus

Embrology

The thymus buds primarily arise from the third pharyngeal pouch bilaterally in the 6th week of gestation. During the 7th and 8th gestational weeks, they elongate and the right and left thymic tissue migrate towards the midline and make contact with each other, and descend to form the thymus gland in the anterior superior mediastinum. Defects during the descent of the thymic buds may result in islands of thymus tissue being left in unrelated anatomical regions. Ectopic thymic tissue can be found in the anterior mediastinal fat (up to 72%), the neck (63%), cardiophrenic angle (21%) and retrocarinal fat [2–4].

The persistence of ectopic thymic tissue is felt to be one of the main reasons for poor outcomes following thymectomy for myasthenia gravis [5, 6]. The frequent presence of ectopic thymic tissue during surgery suggests that removal of as much thymic tissue as possible is necessary during thymectomy for myasthenia gravis.

Surgical Anatomy

An understanding of the anatomy of the thymus is essential for the successful removal of the gland. The thymus is a pinkish gray gland with a lobulated surface with a H-shaped configuration lying anterior to the great vessels. The upper portion usually lies anterior to the left innominate vein as the vein courses across the mediastinum to join the right innominate vein to form the superior vena cava. The cervical horns of the thymus gland project above the suprasternal notch while the inferior horns rest on the pericardium and are connected to it by thin connective tissue. The thymus runs alongside the pleura laterally and is in close proximity with the mediastinal fat and phrenic nerves. Knowledge of the borders of the thymus gland enables the surgeon to understand the extent of resection that should be undertaken when performing a thymectomy. Therefore, a thymectomy should include resection of all thymic and perithymic tissue between the phrenic nerves and from the innominate vein superiorly to the diaphragm inferiorly [7].

The arterial blood supply to the thymus most often arises from the inferior thyroid and

internal mammary arteries. Other sources of arterial blood supply, which have been observed, include the superior thyroid arteries and branches of the subclavian and carotid arteries. Venous drainage of the thymus is predominantly via veins on the posterior aspect of the gland that empties directly into the left innominate vein. In 50% of cases, superior thymic veins drain the superior aspect of the gland and drain into the inferior thyroid vein. Lymphatic drainage of the thymus is to the nodes of the pulmonary hilum and internal mammary chains.

Nervous System

Phrenic Nerves

The phrenic nerves supply sensory fibres to the pericardium and mediastinal pleura, and the diaphragm (motor and sensory). They are formed from the nerve roots of C3, C4 and C5 at the lateral border of the anterior scalenus muscles. The nerves run between the ipsilateral subclavian artery and innominate vein as they enter the superior mediastinum. Within the chest, the nerve passes anterior to the pulmonary hilum along the pericardium.

The pericardiophrenic arteries and veins of the internal mammary vessels travel with the nerves as it courses through the thorax. Both the nerves end with terminal branches at the level of the corresponding hemidiaphragm.

In the chest, the right phrenic nerve crosses the apex of the pleura and descends posterolaterally along the right side of the right innominate vein and external surface of the superior vena cava. It passes anterior to the right hilum, continues over the right side of the pericardium and runs along the inferior vena cava until the diaphragm where it branches.

The left phrenic nerve enters the chest between the left common carotid and subclavian arteries. It crosses the aortic arch laterally and runs in front of the left pulmonary hilum to the diaphragm where it branches.

Vagus Nerves

The vagus nerve exits the skull via the jugular foramen anterior to the jugular vein. It continues to descend through the neck within the carotid sheath where it lies behind the internal carotid artery and internal jugular vein. Each nerve proceeds caudally into the superior mediastinum posterior to its respective sternoclavicular joint and innominate vein.

The right vagus nerve crosses the origin of the right subclavian artery at the sternoclavicular joint and gives off the right recurrent laryngeal nerve that loops around and under the artery. The right recurrent laryngeal nerve reaches the trachea-oesophageal groove behind the common carotid artery and runs parallel to the groove. Within the chest, the right vagus nerve runs posteriorly on the right side of the trachea. It runs behind the right innominate vein, superior vena cava, and pulmonary hilum. At the pulmonary hilum, it divides into posterior pulmonary branches that join with rami from the thoracic sympathetic ganglia to become the right pulmonary plexuses. The right vagus nerve continues onto the oesophagus, where together with the left vagus nerve it forms the oesophgeal plexus.

The left vagus nerve descends into the mediastinum between the left common carotid and left subclavian arteries. Once it reaches the arch of the aorta, it curves posteriorly and crosses the left side of the arch. The left recurrent laryngeal nerve arises from the left vagus at the inferior border of the arch. The nerve hooks below the arch, lateral to the ligamentum arteriosum and runs in the trachea-oesophageal groove to reach the larynx. The left vagus nerve continues its descent posterior to the root of the left lung, where it branches into the left pulmonary plexus.

Thoracic Spinal Nerves

The 12 pairs of thoracic spinal nerves are part of the somatic nervous system, which provides motor and sensory innervation. Each nerve

arises from the spinal cord and exits the spine through intervertebral foramina below its corresponding vertebrae (T1–T12). Each spinal nerve has 4 branches: dorsal ramus, ventral ramus, ramus communicant, and ramus meningeus.

The dorsal ramus runs posteriorly and divides into a medial cutaneous branch and a lateral muscular branch. This supplies the muscles, bones, joints and skin of the back. The ventral ramus is known otherwise as the intercostal nerve. It is covered by the endothoracic fascia and parietal pleura within the intercostal space. The ventral ramus of the 12th spinal nerve is referred to as the subcostal nerve. The ramus communicans connects the thoracic spinal nerves with the sympathetic trunk while the ramus meningeus is a small branch that returns to the spinal canal.

Sympathetic Trunks and Ganglia

The thoracic sympathetic trunk and their ganglia form a large portion of the autonomic nervous system in continuity with the cervical and lumbar sympathetic trunks. It consists of multiple connecting ganglia, lying anterior to the heads of the first to tenth ribs and the bodies of the 11th to 12th thoracic vertebrae, in the posterior part of the mediastinum. The first thoracic sympathetic ganglion is located just above the neck of the first rib and is usually fused with the inferior cervical ganglion to form the cervicothoracic (stellate) ganglion. Anterior to the cervicothoracic ganglion are the vertebral artery and vein. The thoracic sympathetic trunks pierce the diaphragm to enter the abdomen where they join the lumbar sympathetic trunks. Anatomic variations in the sympathetic trunk have been described and are considered to involve the intrathoracic nerve of Kuntz. Kuntz had previously described an inconstant intrathoracic ramus connecting the first and second thoracic nerves, involving sympathetic nerve fibres reaching the brachial plexus without passing through the sympathetic trunk [8]. Postsynaptic sympathetic fibres from the upper thoracic ganglia travel to the thoracic viscera through the cardiopulmonary splanchnic nerves, entering the cardiac, pulmonary and esophageal plexuses. The lower thoracic branches form the lower thoracic splanchnic nerves (greater, lesser and least), descending caudally to the diaphragm to supply the abdominal viscera.

Great Vessels Anatomy

Superior Vena Cava and Innominate Veins

The right internal jugular vein and right subclavian vein unite to form the right innominate vein. This is usually at the level of the sternoclavicular joint where the vein lies anterior to the pleura and vagus nerve. The right innominate vein descends for about 2–3 cm until a point where the pleura, right phrenic nerve and internal mammary artery and vein forms its lateral relationship [9]. Medial to the vein are the thymus gland and brachiocephalic artery. The left innominate vein converges with the right innominate vein at the level of the lower border of the right to form the superior vena cava.

The left innominate vein is twice the length of the right innominate vein as is traverses the mediastinum obliquely from the level of the left sternoclavicular joint to the right first costal cartilage of the right first rib. The right innominate artery, left common carotid artery, left subclavian artery, phrenic and vagus nerves can be found posterior to the left innominate vein.

The superior vena cava formed by the union of the 2 innominate veins descends caudally and drains into the right atrium at the upper border of the 3rd right costal cartilage. The ascending aorta and right innominate artery form its medial relationships and the right phrenic nerve has a direct lateral relationship to this structure. The azygos vein, which is the final tributary of the superior vena cava, passes over the right main bronchus from its posterior course and drains into the superior vena cava near its termination.

Thoracic Aorta and Its Branches

The thoracic aorta arises from the left ventricle at the level of the third sternocostal joint. It ascends slightly towards the right at the level of the second sternocostal joint where it arches obliquely to the left and posteriorly to reach the inferior border of the fourth thoracic vertebra, and descends into the posterior mediastinum to the left of the thoracic vertebra and penetrates the aortic hiatus in the diaphragm at the level of the twelfth thoracic vertebra. Due to the varying course of the thoracic aorta, it can be subdivided into three segments, which are the ascending aorta, the aortic arch, and the descending aorta.

The ascending aorta lies within the fibrous pericardium and is enclosed together with the main pulmonary trunk in a tube of serosal pericardium. Anterior to the lower portion of the ascending aorta are the pulmonary infundibulum and the right auricle. Pericardium and the thymus gland separate the ascending aorta from the sternum superiorly. Posteriorly, the ascending aorta rests on the dome of the left atrium and the right main pulmonary artery. The superior vena cava and main pulmonary artery are located respectively on the right and left sides of the ascending aorta. Lymphatic vessels and the cardiac plexus can be found between the aorta and the main pulmonary artery beneath the serous pericardium.

On average, the length of the ascending aorta varies between 5 and 7 cm and it has a width of 2.5–3 cm. The ascending aorta consists of an aortic root and the tubular ascending aorta. The aortic root extends from the aortic annulus to the sinotubular junction, where the tubular portion of the ascending aorta begins. The following structures make up the aortic root: the aortic annulus, the aortic valve, the sinuses of Valsalva, and the origins of the coronary arteries. This highly complex and sophisticated structure is essential for a competent aortic valve. There are three aortic sinuses and they are named based on their relationship with the coronary arteries: the right, the left, and the noncoronary sinuses. In individuals with bicuspid aortic valves, there are only 2 aortic sinuses present. The sinotubular junction has a diameter of approximately 85% of the diameter of the aortic annulus in normal individuals. The tubular portion of the ascending aorta continues up to the level of the inferior border of the first left sternocostal junction. The tubular portion of the ascending aorta has no branches.

Beneath the lower half of the manubrium, the ascending aorta gives rise to the aortic arch. Initially, the arch ascends diagonally to the left, anterior to the trachea and then descends to the left of the fourth thoracic vertebral body where it continues as the descending thoracic aorta. The aortic arch has a complex relationship with its surrounding structures. The following structures cross the aortic arch deep to the pleura: the left phrenic nerve, left lower cervical cardiac branch of the vagus nerve, left cervical cardiac branch of the sympathetic trunk and left vagus nerve. The left recurrent laryngeal nerve branch from the vagus nerve hooks around the ligamentum arteriosum before ascending obliquely to the superior portion of the distal arch. The following structures are located posterior to the arch from right to left: the trachea and deep cardiac plexus, the left recurrent laryngeal nerve, the oesphagus, the thoracic duct and the vertebral column. The bifurcation of the pulmonary artery is beneath the lower portion of the arch and the ligamentum arteriosum, which is remnant of the ductus arteriosus, connects the lower portion of the arch to either the main or left pulmonary artery. Variations in arch anatomy have been described and are beyond the scope of this chapter.

Three arterial trunks arise from the superior-convex portion of the arch. From anterior to posterior, they are the innominate artery, the left common carotid artery and the left subclavian artery. The left innominate vein crosses these arteries as it courses across the mediastinum. The innominate artery arises at the midpoint of the manubrium and then passes obliquely to the right anterior to the trachea to divide into the right subclavian artery and right common carotid artery at the level of the right sternoclavicular joint. It usually has only terminal branches, although occasionally a thymic

artery or bronchial artery may originate from it. The left common carotid and left subclavian arteries ascend in a semi-spiral fashion to reach the left side of the neck while the vagus nerve descends in the groove formed by these 2 arteries. Posterior to the left tracheal border lie the left recurrent laryngeal nerve, the oesophagus, and the thoracic duct.

The aortic arch continues to become the descending thoracic aorta at the lower border of the fourth thoracic vertebra and passes through the aortic hiatus in the diaphragm anterior to the twelfth thoracic vertebra. Initially, the descending thoracic aorta lies to the left side of the spine. However, at the level of the seventh thoracic vertebra, it lies slightly to the right anterior to the vertebral bodies. Anterior to the descending aorta from superior to inferior are the left pulmonary hilum (pulmonary artery, left main bronchus, and inferior pulmonary vein), the pericardium covering the left atrium, the left oesophagus and the diaphragm. The vertebral column and the hemiazygos vein lie posterior to the descending aorta and the azygos vein and thoracic duct lie on the its right lateral side. The right pleura and lung can be found further laterally while the left lateral side is bordered by the left pleura and lung. The oesophagus crosses anterior to the descending thoracic aorta from right to left.

The arterial blood supply to the pericardium, bronchi, chest wall and oesophagus arise from the descending thoracic aorta. The number, size and origin of bronchial arteries is variable. There are two left bronchial arteries, which arise from the descending thoracic aorta at the level of the 5th thoracic bronchus (upper) and below the level of the left main bronchus (lower). The right bronchial artery does not originate from the descending thoracic aorta. It arises from the third posterior intercostal artery or from the left upper bronchial artery. The descending thoracic aorta also provides a few small pericardial and mediastinal branches that supply the posterior pericardium and connective tissue and lymph nodes located in the posterior mediastinum. The lower thoracic descending aorta provides some branches, which are distributed posterior to the superior surface of the diaphragm.

The first and second posterior intercostal arteries arise from the superior intercostal artery, which is a branch of the costocervical trunk of the subclavian artery. The remaining 9 posterior intercostal arteries originate from the descending aorta. The right posterior intercostal arteries course cross the vertebral bodies and are covered by the right pleura. The left posterior intercostal arteries run behind the hemiazygous and sphlanchnic nerves and then divide into the anterior and posterior rami.

The intercostal arteries are an important source of blood supply for the lower part of the spinal cord. The great artery of Adamkiewicz typically originates from a left intercostal artery in the T8-L1 region and is the primary blood supply to the lower two-thirds of the spinal cord.

The final paired branches of the descending thoracic aorta are the subcostal arteries. They run parallel laterally to the twelfth thoracic vertebral body and enter the abdomen to anastomose with the superior epigastric artery posterior to the arcuate ligament.

Summary

The mediastinum is bounded superiorly by the thoracic inlet, anteriorly by the sternum, posteriorly by the vertebral bodies, laterally by the lungs and inferiorly by the diaphragm. It contains important structures of the circulatory, respiratory, digestive and nervous systems that can be affected by different disease processes. Therefore, it is essential for the thoracic surgeon to have a clear understanding of the anatomy of the mediastinum.

Self-study

1. The organs found in the anterior mediastinum include:
   A. T4-T5
   B. Heart, Roots of the great vessels, pericardium
   C. Fibrous pericardium
   D. Thymus Gland.

2. The following structures are at risk of injury during mediastinoscopy and biopsy except:
   A. Left recurrent laryngeal nerve
   B. Left pulmonary artery
   C. Superior vena cava
   D. Oesophagus.

Answers

1. The organs found in the anterior mediastinum include:
   A. T4–T5 form the posterior boundary of the mediastinum
   B. Heart, Roots of the great vessels, pericardium are found within the visceral compartment
   C. Fibrous pericardium is found within the visceral compartment
   D. Thymus Gland—CORRECT.
2. The following structures are at risk of injury during mediastinoscopy and biopsy except:
   A. Left recurrent laryngeal nerve is at risk of injury during biopsy of the left paratracheal node as it runs in the tracheaoesophageal groove
   B. Left pulmonary artery—CORRECT
   C. Superior vena cava is at risk as it courses towards the right atrium along the anterior aspect of the trachea
   D. Oesophagus is at risk during biopsy of left paratracheal node and subcarinal node as it courses under the trachea.

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Generalities of the Transcervical Approach to the Mediastinum

Josep Belda Sanchis

Key Points

- Be familiar with the anatomy, technical details, and indications of the transcervical approach to the mediastinum.
- Expandable videomediastinoscopes provide a wider surgical field ensuring an optimal and safe exposure of the mediastinal structures.
- Intraoperative monitoring and proper patient positioning and draping of the patient are crucial.
- Keep in mind potential complications during a transcervical approach to the mediastinum:
  - Major hemorrhage is an uncommon but potentially fatal event.
  - Vocal cord palsy due to laryngeal nerve lesion increase the risk of postoperative aspiration pneumonia. Ultrasound and bipolar diathermy devices may be an efficient alternative to electrosurgery to reduce the risk of recurrent laryngeal nerve injury.

Historical Notes

The first indications of the transcervical approach were mainly therapeutic: surgical debridement of mediastinitis (Lurman 1976) [1], thymic pexia to the sternum to relieve shortness of breath (Rehen 1986) [2], resection of hyperplastic thymus gland in patients with myasthenia gravis (Sauerbruch 1911) [2, 3], resection of cystic lesions of the mediastinum [4] and mediastinal parathyroid glands removal [5].

Daniels described in 1949 the biopsy of the supraclavicular and scalene lymph nodes trough a supraclavicular incision to rule out metastasis in patients with lung cancer [6]. Harken in 1954 used a Jackson laryngoscope that was inserted into the mediastinum through a supraclavicular incision to biopsy deeper lymph nodes [7]. Radner described in 1955 a bilateral approach to the paratracheal node chain trough the suprasternal fossa [8], the same approach that Carlens described in 1959 for the mediastinoscopic inspection and tissue biopsy in the superior mediastinum [9]. The coupling of a video camera to the mediastinoscope (Lerut 1989), the design of the two-bladed videomediastinoscope (Linder and Dahan 1992) and the use of a retractor for the elevation of the sternal manubrium [10] have widened enormously the indications of this approach to the mediastinum for staging, diagnostic and therapeutic purposes.

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Description of the Exploration: Equipment Required

The cervical incision and dissection is made with common surgical instruments: a scalpel blade, an electric scalpel, toothless forceps, toothed forceps, Metzenbaum and Mayo scissors, curved Kocher clamps, dissection forceps, a right-angle dissector, Farabeuf's retractors, needle-holders and sutures to ligate small vessels and to close the incision. Although serious complications are exceptionally rare in experienced hands, the necessary equipment to perform a thoracotomy or a median sternotomy should be easily and quickly available.

New energy-based coagulation and cutting devices may be helpful, especially for the en bloc mediastinal lymph node resection. Ultrasound devices and bipolar diathermy devices may be an efficient alternative to electrosurgery to reduce the risk of recurrent laryngeal nerve injury.

Specific instruments for the transcervical approach to the mediastinum are the video mediastinoscopes (Dahan/Linder® videomediastinoscope with distal and parallel expandable blade, Lerut DCI® Video Mediastinoscope and Linder/Hürtgen Distending DCI® Video Mediastinoscope) (Fig. 1), the U-shaped mediastinoscope retaining arm (Fig. 2), the self-retaining sternal retractor to elevate the sternum (Fig. 3), the dissection-coagulation-aspiration tube, a peanut gauze holder, a glass cannula for test aspiration, dissecting, clipping and grasping forceps, biopsy forceps and scissors.

Distal and parallel expandable mediastinoscopes provide a wider surgical field ensuring an optimal exposure of the mediastinal structures; this, combined with a greater freedom of movement, an integrated irrigation and suction channel and atraumatic blades, facilitates the safe advancement of the mediastinoscope along the whole length of the tracheobronchial tree.

The advent of endoscopic-assisted surgical methods has greatly increased the indications of the transcervical approach to the mediastinum over the past decades. Coupling a video camera and a recording system provides a wider operative field and a magnified image, which makes exploration more comfortable and allows to share the procedure and use it for teaching purposes.

Intraoperative Monitoring

The transcervical approach to the mediastinum is done under deep general anesthesia because coughing or moving during the procedure could be hazardous. Specific anesthetic risks of the

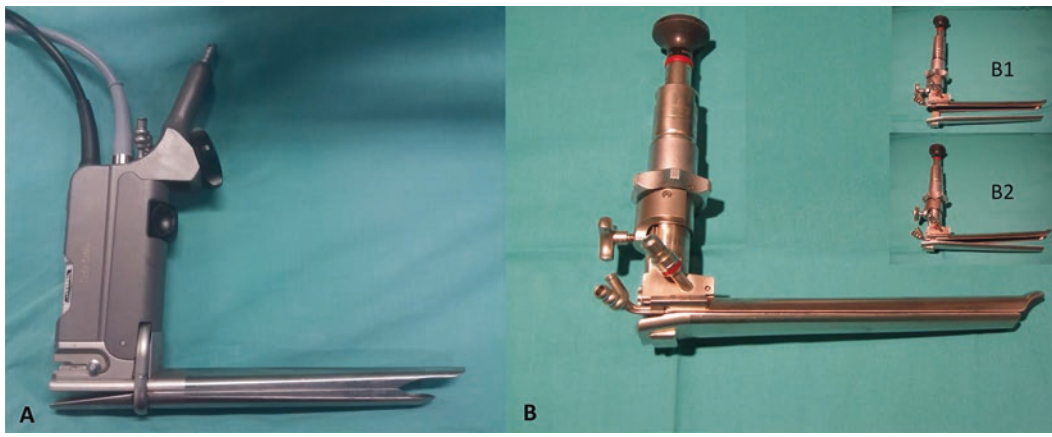

Fig. 1 Linder/Hürtgen Distending DCI® Video Mediastinoscope by Kral Storz, Tuttlingen, Germany (**a**) and Dahan/Linder® Video Mediastinoscope (**b**) with parallel (B1) and distal distal (B2) expandable blades by Richard Wolf, Knittlingen, Germany

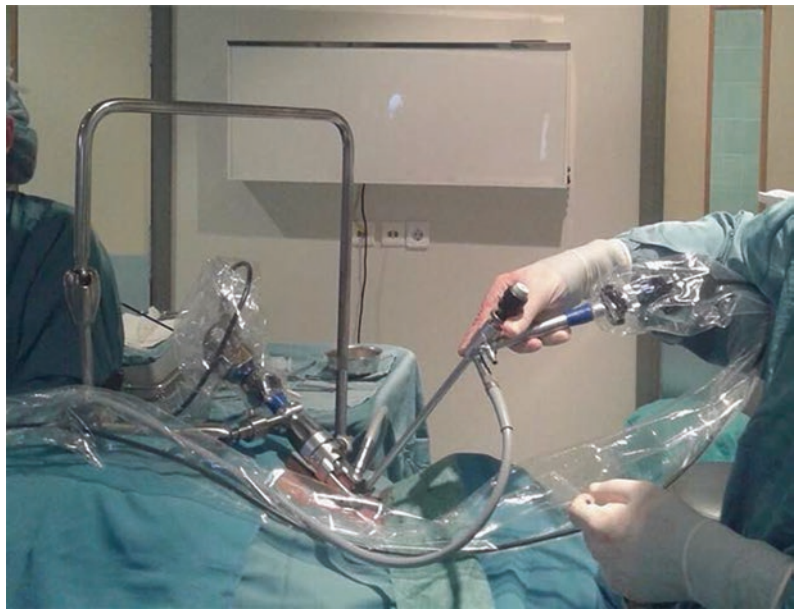

Fig. 2 U-shaped retaining arm with special clamping device used to fix and stabilize the video mediastinoscope during a videomediastinopleuroscopy

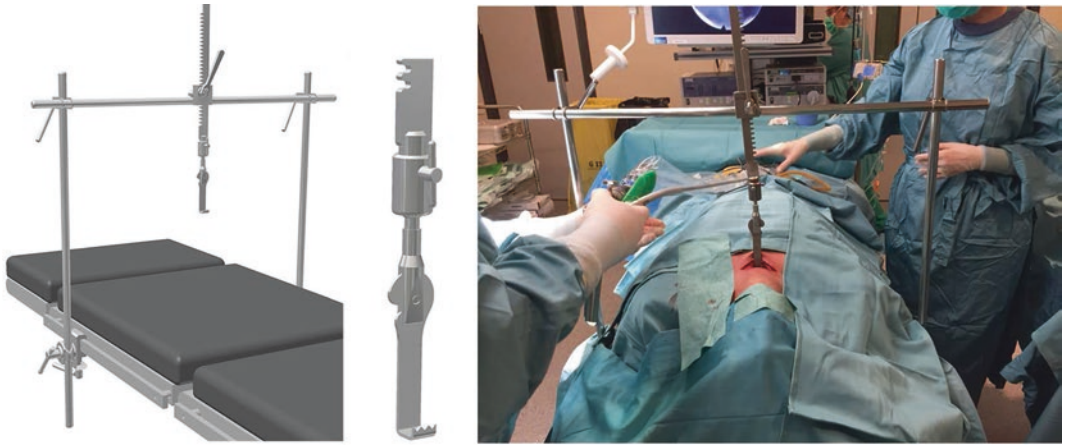

Fig. 3 Sternum Retractor System—Mod. 8750®. Manufactured by Ansabere Surgical, S. L. Developed in collaboration with Dr. José Belda from the Hospital Universitari MútuaTerrassa. Spain (**a**). Sternum retractor elevating the sternum during a transcervical thymectomy

procedure are mainly related to the difficulty of intubation and ventilation, the compression of the innominate artery by the mediastinoscope or, of either the superior vena cava, heart or trachea by anterior mediastinal masses after induction, vagally mediated reflex bradycardia when manipulating the trachea or aorta, and major hemorrhages. A detailed description of the anesthetic considerations during this procedure is beyond the scope of this text, nevertheless some points related to the intraoperative monitoring should be kept in mind:

- Patients with extrinsic obstruction of the trachea may benefit from awake intubation.
- Anesthesia for patients with large mediastinal masses may be associated with significant respiratory and cardiovascular difficulties.
- Reinforced endotracheal tubes are specifically designed to reduce the risk of airway compression during the procedure [11].
- A large bore intravenous line should be secured, preferably in the lower limb.
- The prolonged compression of the innominate artery by the mediastinoscope can lead to a cerebral ischemia. Monitoring O_2 saturation and amplitude of the pulse wave on the right superior hand allows the anesthesiologist and the surgeon to promptly recognize its compression and may obviate the need for radial artery cannulation during the procedure [12].
- Non-invasive blood pressure monitoring is placed on the left arm.
- Electrodes of the EKG are attached to the lateral chest wall or the back, thus liberating the anterior part of the thorax.

Positioning and Draping of the Patient

Proper patient positioning for transcervical access to the mediastinum is crucial. Patient's medical history, physical exam and computed tomography scan will give us informations about cervical rigidity that can lead to with limited neck extension and or on the presence of any mediastinal mass, particularly in the anterior mediastinum, that may affect positioning of the patient on the surgical table.

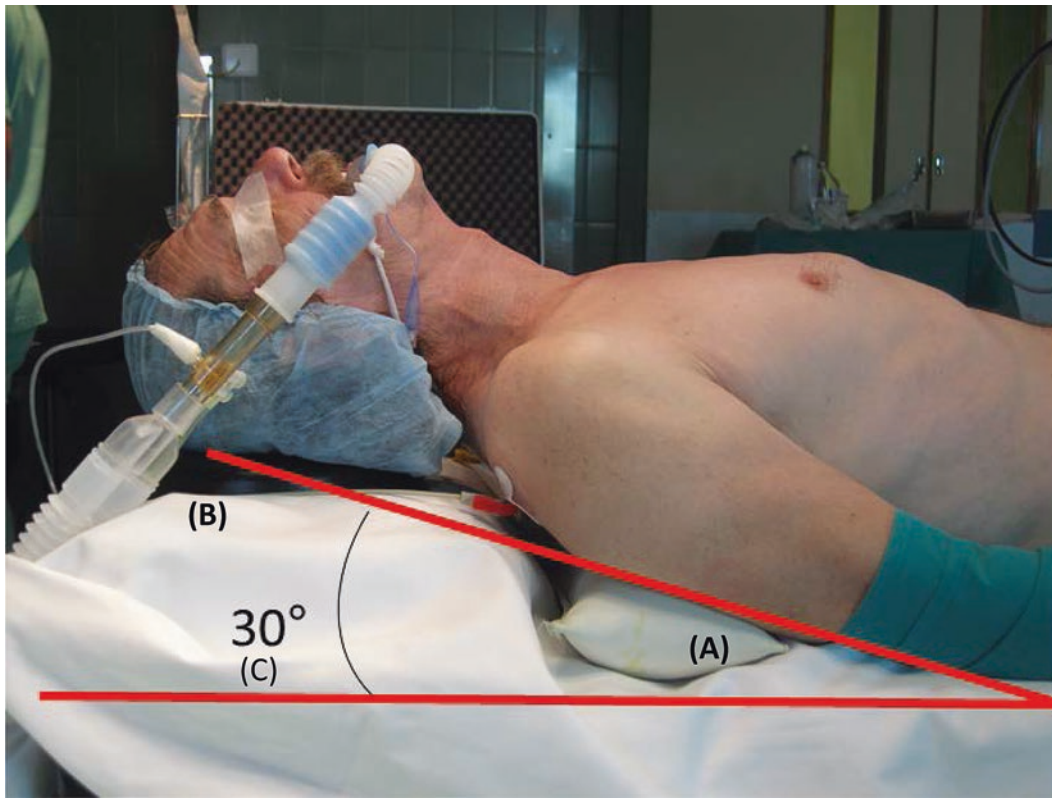

Fig. 4 Patient placed in the supine position with the head at the edge of the operative table. Cushion placed under the shoulders to hyperextend the neck (**a**). Circular pillow to stabilize the patient's head (**b**). Low Fowler's position with the head elevated to 30º (**c**)

Fig. 5 Operative field prepared for median sternotomy (**a**). The additional drape (**b**) is easily removed if median sternotomy is needed

The patient is placed in the supine position with the head at the edge of the operative table. A cushion is placed under the shoulders to hyperextend the neck. A circular pillow is used to help stabilize the patient's head. Depending on the procedure a low Fowler position (i.e. head elevated by 15–30°) may be helpful (Fig. 4).

After cleaning with soap and water, surgical skin preparation should be performed as for median sternotomy with chlorhexidine-based or iodine-based solutions. The surgical field should be draped as for a standard median sternotomy (Fig. 5).

Cervical Incision

The transcervical approach utilizes a horizontal incision just above the sternal notch when neck is hyperextended. The size of the incision is determined by the type of procedure and ranges between 4 and 8 cm. Various thoracic surgical procedures, including transcervical lung resections, mediastinal lymphadenectomies and anterior mediastinal tumor resections will benefit from the elevation of the sternum by a self-retaining sternal retractor. The retraction creates a space underneath the sternum, widening the access to the mediastinum and facilitating the combination of an open and endoscopic procedure (Fig. 3).

The incision is carried out through the subcutaneous fat and the platysma muscle, anterior jugular veins ligated if necessary and the sternohyoid and sternothyroid muscles separated and pulled laterally form the midline. If necessary, the thyroid gland is retracted cranially to expose the trachea. The pretracheal dissection must be performed through the midline being this an avascular plane. After cutting the median cervical aponeurosis, the anterior tracheal wall is identified and the paratracheal fascia can be opened, with scissors if necessary, exposing the anterior wall of the trachea. Blunt digital dissection beneath the pretracheal fascia is then performed as far as possible, following the anterior and lateral faces of the trachea. Careful palpation permits to identify the pulse of the brachiocephalic artery anteriorly, and the one of the aortic arch on the left. Both arteries can be gently palpated with the index finger to check for atheromatous plaques (Fig. 6).

Maneuvers for deliberate exposure and visualization the recurrent laryngeal nerve (during surgery) may reduce the risk of its lesion. Being familiar with the trajectory and surgical relationships between the recurrent nerve and the Berry's ligament, trachea, great vessels and esophagus may help in reducing accidental injuries to it (Fig. 6).

In selected cases, mainly for surgical treatment of substernal goitre, dividing strap muscles could be necessary to obtain a better exposure; they can then be sutured at the end of the operation.

At the end of the procedure the incision is closed in a standard fashion with no need for a drainage. Suturing of the pretracheal muscles

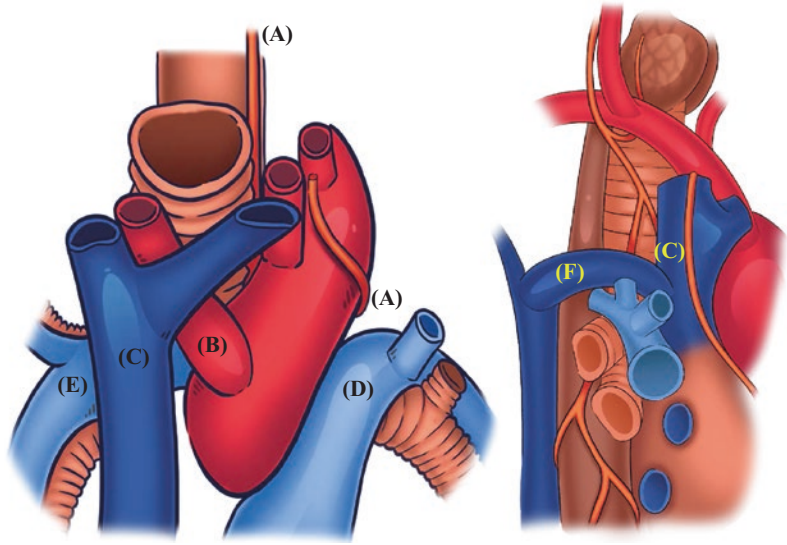

Fig. 6 Anatomical landmarks to keep in mind while performing a transcervical approach to the mediastinum: **a** The left recurrent nerve turns posteriorly around the aortic arch and ascends within the tracheoesophageal groove. **b** Brachiocephalic artery (innominate artery). **c** Superior vena cava. **d** Left pulmonary artery. **e** Right pulmonary artery. **f** Azygos vein

on the midline is not necessary. The subcutaneous tissue and the platysma are closed separately with running absorbable sutures.

Indications of the Transcervical Approach to the Mediastinum

The transcervical approach, with or without elevation of the sternum, allows to perform a significant number of diagnostic and therapeutic procedures. In addition, this approach can be combined with a subxiphoid or a VATS approach improving increasing the therapeutic and diagnostic possibilities without increasing the risk [13].

Diagnostic indications

- Diagnosis, staging and restaging of lung cancer [14–21].
- Mediastinal and pleural staging of mesothelioma [22–28].
- Diagnosis of hematological malignancies and other solid tumors of the mediastinum [29].
- Diagnosis of intrathoracic infections and inflammations [30].

Therapeutic indications

- Thymectomy in patients with or without myasthenia gravis [10, 31–58].
- Resection of cervico-mediastinal goiters, ectopic mediastinal goiter and mediastinal lymph node metastases in thyroid cancer [59–74].
- Drainage of mediastinal abscesses and descending necrotizing mediastinitis [75–83].
- Removal of foreign bodies [84–87].
- Esophageal diseases [88–100].
- Resection of ectopic mediastinal parathyroid adenoma [101–110].
- Resection and drainage of mediastinal cysts [111–120].
- Miscelanea: airway repair, pulmonary resections, tracheal and bronchial release, pleurodesis [16, 121–140].

Technical Variants of the Transcervical Approach to the Mediastinum

New technologies allow to increase the potential of the transcervical approach. In addition, its complement action with other approaches, minimally invasive or not, improves the surgical exposure permitting to undertake more complex lesion, thoracic and mediastinal, in a safer and more effective fashion. A multidisciplinary team and surgical subspecialization is often required to successful undertake these lesions.

- Classical and extended videomediastinoscopy.
- Retrosternal or prevascular mediastinoscopy.
- Video-Assisted Mediastinoscopic Lymphadenectomy (VAMLA).
- Transcervical Extended Mediastinal Lymphadenectomy (TEMLA).
- Cervical Mediastino-Thoracoscopy (CMT).
- Cervical Incision Thoracic Endoscopic Surgery (CITES).
- Cervical Video-Assisted Thoracoscopic Surgery (C-VATS).
- Transcervical-subxiphoid approach.
- Transcervical-uni or bilateral transthoracic (VATS) approach.
- Transcervical-open transcostal (thoracotomy) approach.
- Transcervical-transhiatal approach.
- Transcervical–transsternal approach.

Contraindications

Contraindications of the transcervical approach to the mediastinum may be categorized as general or specific as well as relative or absolute. Relative contraindications require a careful balancing of the risks and are often dependent on operator's and center/team expertise. In addition, contraindications may relate to individual factors and to the type of surgical procedure.

Aneurism of the aortic arch and severe calcified atheromatous plaques in the brachiocephalic artery and the aortic arch constitute an absolute contraindication of the surgical exploration of the mediastinum (e.g. mediastinoscopy, TEMLA, VAMLA) mainly due to the embolic risk.

Coagulation tests should be performed preoperatively in order to identify and correct any alteration.

Cervical rigidity and large goitres are relative contraindications for the transcervical surgical exploration of the mediastinum with diagnostic or staging purposes. Superior vena cava syndrome and tracheostomy do not represent a contraindication [141–145]. Previous mediastinal surgery, including sternotomy, is a relative contraindication. In these patients, an initial attempt should be made to assess whether the exploration can be performed safely [146].

Previous classical mediastinoscopy or mediastinal radiotherapy does not contraindicate a remediastinoscopy, although, the increased adhesions caused by the previous mediastinoscopy can result in a more arduous and hazardous surgery. Frequently, the brachiocephalic artery is densely adherent to the anterior wall of the trachea, making dissection in this area the most dangerous point of the procedure. In this case, it is recommended to bluntly create a tunnel on the left side of the trachea with the finger and continue dissecting downward very gently [147–152].

Cervical mediastino-thoracoscopy (CMT), cervical incision thoracic endoscopic surgery (CITES) and cervical video-assisted thoracoscopic surgery (C-VATS) are contraindicated in patients with bulky pleural tumor on mediastinal surface in MPM, pulmonary tumors invading the upper part of the mediastinum and mediastinal or pleural adhesions due to previous radiotherapy, surgery or infection [153–155].

Transcervical thymectomy should be contraindicated in patients with tumors of the anterior mediastinum greater than 5 cm. [32, 47, 156]. Malignant tumors of mediastinum requiring extensive dissection and/or extended resection of neighbour tissues/organs cannot be approached safely by the transcervical access [157].

Complications of the Transcervical Approach to the Mediastinum

The most relevant complications of the transcervical approach to the mediastinum are the major hemorrhage secondary to the injury to the great mediastinal vessels and the lesion of the recurrent laryngeal nerve. Other complications include the damage to the airway, esophagus, phrenic nerve and thoracic duct (resulting in a mediastinal chyloma and chylothorax), wound infection, mediastinitis, mediastinal hematoma, pneumothorax and hemothorax, surgical wound seeding with tumor cells and cerebrovascular accident.

Major hemorrhage during mediastinoscopy is an uncommon but potentially fatal event and remains the most feared complication. The reported pooled rate of major hemorrhage is 0.3% [158–169]. The most frequently injured vessels are the azygos vein and the innominate or the pulmonary arteries. Factors that may potentially increase the risk of a major bleeding are prior mediastinal radiotherapy and surgery, and superior vena cava syndrome. Also, some underlying conditions may significantly increase the risk of hemorrhage, for example, chronic pulmonary inflammatory disorders, such as bronchiectasis, tuberculosis and chronic bronchitis that may be associated with hypertrophied bronchial arteries and increase in the collateral supply from systemic vessels to the pathologic lung parenchyma.

When in doubt, needle puncture aspiration should be performed before forceps biopsy to avoid "biopsy" of vessels.

The management of major hemorrhage during mediastinoscopy is not standardized. The initial control could be achieved by direct compression: digital or with the mediastinoscope (arterial hemorrhage), sponge forceps or small packing (bleeding from low-pressure vessels, e.g. azygos, cava and pulmonary artery). Small vessels can be controlled by energy-based vessel sealing systems and vascular clips.

At the same time, the instruments for a median sternotomy or thoracotomy should be prepared. Patients should undergo open exploration (or conversion) after one or more attempts at hemostasis with packing alone over a period of 20–45 minutes each. With these maneuvers, the control rate of the hemorrhage is superior to 90% [158]. If necessary, packing should be left in place while single lung ventilation is established and the patient repositioned.

Decision regarding surgical exploration for definitive control of hemorrhage should be individualized. The most appropriate approach (sternotomy or thoracotomy) should depend on the site of injury and status of the mediastinum. A median sternotomy provides excellent access to the brachiocephalic artery and the anterior part of the superior vena cava. If hemorrhage is suspected to derive from the azygos vein, posterior superior vena cava, or pulmonary artery, a standard right posterolateral thoracotomy provides excellent exposure for all of them.

Patients with atheromatous disease are at risk for stroke if there is significant compression of the innominate artery or the aortic arch during an extended cervical mediastinoscopy [168]. Traumatic pseudoaneurysm of the brachiocephalic artery following medianoscopy has been described. Initial endovascular stent placement should be attempted before surgical repair [169–172].

Incisional metastasis of a lung cancer after a mediastinoscopy is an extremely rare complication. Removal of gauze inside the scope during the procedure could be useful to avoid this complication [173–177].

A serious but rare complication is the injury of the esophagus. In order to reduce the risk of its injury, precise and careful use of electrosurgical devices is recommended. Early recognition and treatment is imperative to prevent cervicomediastinitis. In addition to the parenteral nutrition, antibiotics, and drainage of the mediastinum through the mediastinoscopy incision, management algorithms include primary surgical repair, that can be attempted if diagnosed immediately, and esophageal exclusion with stent placement [178, 179].

Injuries to the tracheobronchial tree during a transcervical approach to the mediastinum are rare with a reported incidence of 0.1% [127].

Electrosurgical devices (including the suction-coagulation cannula) have to be used with caution during dissection and coagulation to prevent tracheobronchial wall necrosis. Ultrasound devices may be a good alternative to electrosurgery especially during subcarinal dissection. Transcervical (even mediastinoscopic) repair is possible and should be considered before undergoing a thoracotomy [127, 128, 165, 180].

Vocal cord palsy can be either temporary or permanent. Incidence of laryngeal nerve lesion during the transcervical approach to the mediastinum ranges between 2 and 5% [181–186].

In addition to the vocal cord dysfunction (the vocal cord remain in the abducted position), injury to the recurrent laryngeal nerve has been associated to pharyngeal dysphagia due to a partial dysfunction of cricopharingeal muscles. These conditions greatly increase the risk of aspiration pneumonia, especially after lung resection [187].

Depending on the procedure, intraoperative visualization of left or both laryngeal recurrent nerves is mandatory. Some tips may help to avoid injuring this nerve: once identified, it should be gently manipulated and dissected from the surrounding tissue, preserving the fascia covering its medial surface; as well, ultrasound and bipolar diathermy devices may be an efficient alternative to electrosurgery to reduce the risk of injury. It has also been described intraoperative recurrent laryngeal nerve monitoring during mediastinoscopy [183, 186].

Vocal cord palsy could be temporary and recover on their own within a few weeks or months. Treatment options for definitive palsy include voice therapy and injectable implants into the region of the vocal cords to achieve fold medialization.

Self-study

Which of the following statements is true regarding the transcervical approach to the mediastinum?

(a) Previous radiotherapy is always a contraindication
(b) The most relevant complication is the major hemorrhage
(c) It could be done under general anesthesia or mild sedations depending on the estimated duration of the procedure
(d) O_2 saturation and amplitude of the pulse wave should be monitored on the left hand.

Which of the following statements is false regarding the transcervical approach to the mediastinum?

(a) Patients with extrinsic obstruction of the trachea may benefit from awake intubation.
(b) Aneurism and severe calcified atheromatous plaques in the brachiocephalic artery and the aortic arch constitute an absolute contraindication
(c) The most frequently injured vessels are the azygos vein and the pulmonary artery
(d) Initial control of a hemorrhage could be achieved with clamps or sutures.

Answers

Which of the following statements is true regarding the transcervical approach to the mediastinum?

(a) Previous radiotherapy is always a contraindication. **Not always**.
(b) The most relevant complication is the major hemorrhage. **CORRECT**.
(c) It could be done under general anesthesia or mild sedations depending on the estimated duration of the procedure. **Never a transcervical approach to the mediastinum under sedation, coughing or moving during the procedure could be hazardous**.
(d) O_2 saturation and amplitude of the pulse wave should be monitored on the left hand. **The compression of the innominate artery by the mediastinoscope can lead to a cerebral ischemia. Monitoring O2 saturation and amplitude of the pulse wave on the right (not left) superior hand allows the anesthesiologist and the surgeon to promptly recognize its compression**.

Which of the following statements is false regarding the transcervical approach to the mediastinum?

(a) Patients with extrinsic obstruction of the trachea may benefit from awake intubation. **This is true. In patients with large mediastinal mass, muscle relaxation at the time of induction could significantly worsen any cardiac or airway compression. When concern for airway or compression exists, awake fiberoptic intubation should be taken in mind.**

(b) Aneurism and severe calcified atheromatous plaques in the brachiocephalic artery and the aortic arch constitute an absolute contraindication. **This is true.**

(c) The most frequently injured vessels are the azygos vein and the pulmonary artery. **This is true.**

(d) Initial control of a hemorrhage could be achieved with clamps or sutures. **This statement is false, then this is the CORRECT answer. The initial control should be achieved by direct compression (digital, with the mediastinoscope, sponge forceps or small packing**.

Compliance with Ethical Requirements

Conflict of Interest

José Belda Sanchis declares that he has no conflict of interest.

Informed Consent

Additional informed consent was obtained from all patients for which identifying information is included in this article.

No animal or human studies were carried out by the authors for this article.

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Approaches and Surgical Techniques in the Thymus Pathology

Francesca Calabrese and Piergiorgio Solli

Key Points

- The thymus is the site of origin of benign and malignant neoplasms.
- Median sternotomy has been considered the standard approach for many years.
- VATS and RATS have gained a relevant role for benign diseases and early stage thymic tumors.

Introduction

The thymus gland still continues to present challenges to thoracic surgeons. The thymus is the site of origin of benign and malignant neoplasms; it also is involved in specific aspects of cellular immunity.

It is necessary to differentiate between thymic pathologies, ranging from thymic hyperplasia associated or not with myasthenia gravis to the thymic neoplasms (thymomas).

Thymic tumors are rare diseases with a reported annual incidence ranging from 1.3 to 3.2/million and still represent the most common anterior mediastinal tumors in the adults. They are classified using the recommendations of the World Health Organization (WHO) into thymomas—further divided into low-grade (A, AB) and high-grade (B1, B2, B3)—thymic carcinomas (TC) and thymic tumors with neuroendocrine features (NETT) [1].

After a period of relatively indolent interest in the study of these thymic malignancies, the last 20 years have represented an era of incredible improvements in the diagnosis, classification, staging and management of these rare tumors, though surgery still represents the treatment of choice in thymic tumors and complete resection still is considered the gold standard.

The anatomical location of the thymus in the anterior mediastinum has convinced along years the thoracic surgeons that median sternotomy was the only conceivable surgical approach which may provide a complete resection; in the past alternative techniques (cervical incisions only or thoracotomy) were less utilized and often criticized for the perceived high chance not to achieve a complete resection.

Surgical approaches for thymectomy include a large variety of procedures: trans-sternal and trans-cervical approach as well as a assortment of minimally invasive techniques. Regardless of the approach, the basic principles of thymic radical resection should include: mediastinal exploration, en bloc resection of the thymus gland including the cervical poles and adjacent mediastinal fat, protection of the phrenic nerves, and the prevention of intrapleural dissemination.

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For patients with thymoma, whilst a median sternotomy has been traditionally used, currently minimally-invasive techniques (MIT) including video-assisted (VATS) and robotic-assisted thoracic surgery (RATS) are now considered the standard of care in early-stage thymic tumors [1].

For patients without a thymoma nevertheless requiring thymectomy (hyperplasia associated with myasthenia gravis, benign conditions), MIT represent the gold standard. Less commonly the resection could be achieved through a partial sternotomy (manubrium split) again occasionally associated to VATS (or RATS).

The present chapter will focus on the following surgical topics: (a) standard thymectomy (trans-sternal approach); (b) trans-cervical approach; (c) VATS thymectomy; (d) Robotic thymectomy (RATS) and (d) general consideration on MIT versus open approach.

Standard Trans-sternal Thymectomy

Radical thymectomy through complete vertical sternotomy with cervical extension has been initially described by Jaretzki and Coll [2] and advocated by Masaoka et al. [3] in their landmark publications.

A radical thymectomy can be accomplished using a partial sternal-splitting incision (just the upper part at the level of the manubrium) or classically a complete sternotomy, mostly according to thymoma's dimension and topography.

It should be noted that when the indication to surgery is a thymic tumors, a complete sternotomy is usually mandatory and should be considered the standard approach. The more conservative sternal splitting should be reserved to benign conditions and should be utilized very carefully in the contest of myasthenia gravis when a total thymectomy is nevertheless the target. Most of the surgical details are shared between the two approaches with only limited differences.

Surgical Technique

With general endotracheal anesthesia using a single-lumen or better a double lumen endotracheal tube, the patient is placed in the supine position with the neck extension; neck, chest and upper abdomen are prepped and draped.

Usually, the upper end of the skin incision is kept one to two finger below the sternal notch and carried down vertically to the level of the 3rd–5th intercostal space (splitting) or to the level of the xiphoid process.

With cephalad skin retraction, the sternal notch is dissected free so that a finger can be placed beneath the manubrium, then the sternum is longitudinally divided till the xiphoid process (or just split in the upper third) using a micro-sagittal or oscillatory saw according to surgeon's preference. At this stage the sternal spreader (or manubrium spreader) can be put in place offering the surgical field for the completion of the procedure.

Through this relatively short skin incision, after complete (or partial) division of the sternum, adequate visualization of the entire mediastinal portion of the thymus and its cervical extension can be normally obtained.

The overlying mediastinal pleura is separated in the midline, exposing the thymus gland and the left innominate vein. Both pleural spaces can be opened, making sure to identify and protect both phrenic nerves especially in the cephalic area; identification of the internal thoracic vein provides a useful landmark for the superior extent of the pleural opening, since the phrenic nerve is in its immediate proximity.

Exploration of the central mediastinal area, both pleural spaces and both lungs should be routinely performed before starting any dissection.

Thymectomy is usually begun by dissecting the middle of the right inferior horn off the pericardium. Utilizing a right-angle clamp in a progressive "walking" technique, the inferior horn is firstly dissected in a caudal direction down to the pericardial fat pad, which is then clamped and divided (small vessels can be present).

With the right-angle clamp still on the inferior horn, used to expose/retract the specimen, the right lobe of the thymus is dissected off the pericardium in a cephalad direction. This dissection is discontinued at the midportion of the thymus and subsequently focused on the right superior horn in the cervical area. The right superior horn is circumferentially freed, again utilizing a right-angle clamp in a walking technique until the thyro-thymic ligament is seen. The right superior horn is then disconnected from the thyroid gland surrounding tissue and dividing the above mentioned ligament (titanium or polymeric clips, ligating it with 2-0 silk or with biothermal sealer). At this stage the thymus gland is pulled medially with both the upper and lower clamps and all the middle portion of the right lobe and associated fatty tissue are pulled back from the area of the phrenic nerve up to the junction of the left innominate vein and superior vena cava. The lateral arterial vessels arising from the internal mammary artery are very carefully cauterized or ligated so as to avoid inadvertent injury to the phrenic nerve. Oozing in the area of the phrenic nerve can be controlled with gauze packing. The thymus gland is now further reflected along the left innominate vein until the midline venous drainage is identified. The same steps are now carried out on the left side.

Notably, the left sided dissection could be more problematic because the phrenic nerve tends to come closer, and there seems to be a greater amount of fatty tissue obscuring its visualization. Again, a blunt dissection technique in the critical midportion of the thymus where the nerve and thymus are in closest proximity helps prevent nerve's injury.

Once all of the horns have been successfully ligated and the midportions of the gland dissected free, the central venous drainage (Keynes veins) is divided (again according to preference with titanium or polymeric clips, ligating it with 2-0 silk or with biothermal sealer).

If the surgeon encounters unusual thymic adherence or infiltration to surrounding structures such as the pericardium, adjacent lung parenchyma, vagus and phrenic nerves, superior vena cava system's veins, these should be resected en-bloc with the thymus. If the extent of the thymus gland cannot be discriminated during dissection, separate margins are sent for frozen-section analysis to be sure no thymic tissue is left behind.

Following completion of total thymectomy ("from one phrenic nerve to the other ones" as described by Jaretzki), meticulous hemostasis is obtained with attention again paid to visualizing the phrenic nerves.

Usually two chest tubes are placed (one in each hemithorax, aiming to prevent pleural fluid accumulation more than for parenchyma air-leaking). The sternum is re-approximated with interrupted stiches (absorbable or steel wires), with two or three wires placed into the manubrium and the remaining around the sternal interspaces. The remaining soft tissue is closed with multiple layers of running absorbable suture, including a subcuticular skin closure (soft tissue closure should be very meticulous to prevent infection very risky in this area).

In the case of large thymic tumors with locally advanced extension, the sternal incision could result of being insufficient and a larger additional incision could be mandatory. A wider approach is usually obtained with an associated thoracotomy (hemi-clamshell incision) especially in case of thymic carcinoma invading mediastinal structure and/or when extracorporeal support should be considered [4, 5].

Transcervical Thymectomy

The transcervical thymectomy (TCT) was developed primarily for excision of the thymus gland in patients suffering from myasthenia gravis (MG). The basic trans-cervical resection involves an intracapsular removal of the mediastinal thymus via a cervical incision and is limited to removing the central cervical-mediastinal lobes. The extended resection described by Cooper et al. [6] in 1988 employs a special manubrial retractor to improve exposure of the mediastinum. All visible mediastinal thymic tissue is removed with dissection extending in the extracapsular plane.

After general anesthesia is induced and a single-lumen endotracheal tube placed, the patient is placed in a supine position with the neck hyper-extended by placement of an inflatable bag beneath the shoulders.

The neck and upper chest are prepared and draped. A curved, transverse collar skin incision is placed about 2 cm above the sternal notch and extended for 5 cm along the skin folds. After elevating platysma flaps, the sternohyoid and sternothyroid muscles are separated in the midline and the superior poles of the thymus gland are found on the posterior surface of the strap muscles, anterior to the inferior thyroid veins. The superior poles of the gland are dissected out and are followed up to their termination. Silk ties can be used to ligate each superior pole, and subsequently each tie can be used to manipulate the thymus during the operation. The substernal plane can be freed by bluntly pushing the anterior mediastinal tissues away from the sternum.

The remainder of the operation entails using blunt dissection to lift the thymus gland off the left innominate vein, pericardium and pleura. Individual thymic venous branches are ligated. Once the gland has been dissected off the innominate vein, the manubrial retractor is placed into the sternal notch and can be used to expose the remainder of the anterior mediastinum. The dissection is performed bluntly using peanuts or sponges. The goal is to sweep the gland off of the pleural edges laterally, the sternum anteriorly and the pericardium posteriorly without affecting both the phrenic nerves. With slow persistence, the gland can be safely mobilized from the mediastinum bringing the inferior aspect of the gland up into the neck. The wound is closed in several layers. A red rubber catheter can be placed in the mediastinum/pleural space if there is any concern of having entered the pleural cavity. The patient can be generally extubated immediately after the procedure and - providing a chest X-ray confirming no pneumothorax and bilateral lung expansion—the patient can be discharged home soon (in the idea of the Authors even within 6 hours after the operation).

As mentioned in the introduction, the cervical approach has gained popularity in the early ‘90s for the minimal surgical trauma and cosmetic result If compared to sternotomy, nevertheless its use has remained limited to benign conditions or mostly to hyperplasia and associated myasthenia gravis, given the very limited exposure that can be achieved with this small collar incision with only partial access to the lower portion of the thymus gland.

VATS Thymectomy

There is a large number of variations in the type of video assisted thoracoscopic techniques that have been developed in order to assist in the performance of a radical thymectomy [7].

The classic VATS technique is described and includes an unilateral video-endoscopic exposure of the anterior mediastinum (from the right or from the left, both the approach have been described in the literature with a slight preference for the left side).

General anesthesia and a double-lumen endotracheal tube are required, the patient is placed in right (or left) lateral site normally with a 30° lateral decubitus position. A gentle controlled CO_2 insufflation is normally reported as standard practice by the vast majority of Authors (between 6 and 8 mmHg).

A three-port technique is normally required but there are many report with 2- or 4-ports or with the uniportal technique; a 10 mm or 5 mm HD camera could be employed, usually with the 30° visual angle.

Ports are placed just in front of the tip of the scapula along the posterior axillary line (first), second and third ports are inserted under direct vision at the level of the 3rd intercostal space midaxillary line and the 5th–6th space anterior axillary line. The camera and the instruments can freely exchange during the entire procedure according to the level and complexity of dissection. Currently most surgeons use biothermal vessel sealer for a quicker and more expeditious dissection.

The entire hemi-thorax is carefully examined and the major structural landmarks should be identified: the inferior horns of the thymus

are identified over the pericardium, both the phrenic nerves should be clearly visualized, the superior vena cava and the left innominate vein recognized (according to left or right preferred approach), the orientation of the tumors should be assessed together with its relationship with the upper hornes (most complicated step of the procedure).

The dissection is begun caudally, following the mediastinal pleura just anteriorly to the phrenic nerve and continued cephalad to the junction of the superior vena cava and innominate vein (on the right) or to the level of the left innominate vein (on the left). The thymic venous tributaries (Keynes) draining into the left brachiocephalic vein are identified and divided (polymeric or metallic clips, vessel sealer).

Dissection is then carried behind the sternum with gentle traction on the thymus, both the inferior horns are followed and dissected up to the thymus isthmus.

The most difficult part is the dissection of the superior horns due to the risk of vascular injury to the superior vena cava and the innominate veins. With moderate traction of the thymus, both the superior horns can be carefully dissected from their fascial attachments mainly using blunt dissection. They lay on both side anteriorly to innominate veins but not rarely—especially the left superior horn—can identified behind instead of in front of the brachiocephalic vein, hence it should be paid attention to this anatomic variation.

The totally freed thymus gland (thymoma en-bloc with all the anterior mediastinal soft tissue including all the pericardial fat) is eventually removed within a protected plastic bag in order to prevent ports from tumor cells seeding.

The specimen when outside the thorax and before being sent to pathology has to be carefully inspected for macroscopic completeness of resection [8]. The anterior mediastinum is inspected for hemostasis, a chest tube is positioned and the lung re-inflated under vision.

Some Authors advocate a bilateral VATS approach technique for an ameliorated vison and improved recognition of structures within the anterior mediastinum (especially the contralateral phrenic nerve and innominate veins) and also for the chance to achieve a more radical dissection on both sides (video-assisted thoracoscopic extended thymectomy). Moreover newer techniques have been described (subxyphoid approach with multiple variations) such as the possibility of accomplishing thymus resection without intubation and general anesthesia ("awake tubeless approach"). All these reports provide interesting and charming results but still should be supported by future studies and results.

RATS Thymectomy

The introduction of robotic-assisted surgical technology has been clearly a step forward in evolution of minimally invasive approaches, particularly in this area due to the theoretical technical advantage over standard VATS for surgical application in remote-to-reach or narrow anatomical regions, such as the upper mediastinum.

The surgical technique has been completely standardized by the different groups with large experience in this field, with only negligible differences [9–12].

General anesthesia and double-lumen endotracheal intubation are required. The patient is positioned left- or right-side up (depending on the side of operation based on the surgeon preference) at a 30° angle with a bean bag. The operative field should always be prepared and draped for an eventual conversion to median sternotomy or thoracotomy. A camera port for the 3D 0° or 30° stereo endoscope is introduced through a 15 mm incision on the 5th intercostal space on the midaxillary line and two additional thoracic ports are inserted: one on the 3rd intercostal space on the midaxillary region and another on the 5th intercostal space on the midclavicular space. Two arms of the robotic system are then attached to the two access points and another arm is attached to the port-inserted endoscope. The left arm has a grasper instrument; the right arm has an Endo-dissector device (Intuitive Surgical, Inc.) with electric cautery function (or a harmonic ultrasound dissector)

used to perform the dissection. During surgery, the hemithorax is inflated through the camera port with CO_2 ranging in pressure from 6 to 10 mmHg. When a left-sided approach is performed, the dissection starts inferiorly at the left pericardiophrenic angle and continues along the anterior border of the phrenic nerve. All anterior mediastinal tissue, including fat, is isolated from the phrenic nerve. The left inferior horn of the thymus is then located and dissected from the pericardium. Subsequently, the thymic gland is separated from the retrosternal area until the right mediastinal pleura and the right inferior horn are found. At this point, the lower part of the thymus is mobilized upward, the left innominate vein is identified, and the dissection continues along the border of the innominate vein up to the point where the thymic veins are identified, clipped, and divided. The dissection continues upward to the neck until the superior horns are identified and divided from the inferior portion of the thyroid gland by a blunt dissection. The thymus gland, anterior mediastinal, and neck fatty tissues are radically resected and the specimen is placed in an endobag and removed through trocar incision.

In the right side approach, dissection begins from the cardio-phrenic angle and the mediastinal pleura is incised just anterior and medial to the right phrenic nerve, then it continues upward till all anterior mediastinal tissue is separated from the nerve and the superior vena cava. At this point, the dissection follows the retrosternal area by division of the pleura along the lateral border of the right internal mammary vessels from the origin all the way to the diaphragm. The next step involves elevating the thymus off the pericardium, starting from the inferior horns and heading upward until the left brachiocephalic vein is encountered. The thymus is dissected off the anterior aspect of the vein and the thymic veins are identified, clipped, and dissected. Then, the superior horns are identified and divided from the thyroid gland. The left pleura is then opened and after the left phrenic nerve is identified, the dissection of the thymus is completed.

After the hemostasis, a 28F drainage tube is inserted through the port of the 5th intercostal space, the lung is inflated, and the other wounds are closed.

The better side to perform thymectomy is still a matter of debate. Authors supporting the left-sided approach point out that the left lobe of the thymus gland is usually larger and extends down to the pericardiophrenic area, and that the aorto-pulmonary window and the region below the left innominate vein are frequent sites of ectopic thymic tissue. The thymus may also extend lateral to or under the left phrenic nerve, or descend totally or partially posterior to the innominate vein. Moreover, the right phrenic nerve is protected by the superior vena cava in the high mediastinum and may be identified and easily followed in the lower part.

On the other hand, authors who prefer a right-sided approach describe a larger operative field, a better visualization of the venous confluence by following the superior vena cava, visualization of the aorto-caval groove and a better ergonomic position to accomplish dissection, making it easier in the early part of the learning curve [10, 11].

Regardless of the side, it is important that the approach is tailored on the patient's anatomy in order to perform a complete dissection of the thymic tissue, the mediastinal fat from a phrenic nerve to another, and from the superior horns to the cardio-phrenic recess. Moreover the surgical technique in case of thymoma should be a careful "no-touch" technique without any specimen manipulation in order to prevent the risk of capsule breach and dissemination of the tumor in the pleural cavity and following therefore a safer oncological proof tumor removal.

Minimally Invasive Versus Open Approach: General Considerations

The debate on which approach (open vs. MIT) is the most appropriate for thymic diseases has generated a large body of medical literature, most of which are retrospective small- or single institutional series; no randomized clinical trials

have been designed nor it seems likely to have these in the near future, due to the rarity of the disease and the worldwide rapid adoption of MIT regardless scientific validation.

Some general aspects of common sense for the correct identification of the better surgical approach in thymic tumors are here summarized and could not ignore histology, size and TNM tumor stage along with individual patient's clinical characteristics and surgeon's experience and local facilities (i.e. availability of robotic technology).

According to the European Society of Medical Oncology (ESMO) guidelines [13] the gold standard approach in resectable disease (stage I, stage II and selected stage III tumors according to the Masaoka-Koga classification) still remain median sternotomy, however MIT should be regarded as an option for stage I and II "in the hands of experienced and appropriately trained surgeons".

A very recent retrospective study from Wang et al. [14] based on the Chinese Alliance for Research in Thymomas (ChART) database compared perioperative outcomes and survival in >1000 patients with clinically early-stage (Masaoka I and II) thymic tumors operated between 1994 and 2012, receiving VATS or an open approach.

After a median follow-up time of 33 months, a higher percentage of complete resections was observed in the VATS group; although 5-years overall survival was similar, recurrence-free survival was significantly better in the VATS group (92% vs. 83%). The authors conclude that in early-stage thymic tumors, VATS may offer better peri-operative outcome and non-inferior survival as compared to open approaches.

The size has been traditionally considered a crucial element for the surgical approach, with MIT indicated only for smaller tumors. The cut-off was originally set at 3 cm, then increased to 5 cm. At the same time, thanks to improved technology and modern robot machines allowing a very precise surgical dissection, larger tumors have been reported to be successfully removed using MIT and currently T dimension should not be regarded as an absolute contraindication to MIT, provided that basic oncological principles are followed (preservation of the capsule and radical resection), being indications to MIT more related to the local invasion (great vessels, pericardium) rather than only to tumor dimension.

The body of evidence from most recent literature [15−17] indicates that for early stage thymic tumors, minimally invasive techniques are not inferior to sternotomy, with improved results in terms of shorter length of stay, reduced intraoperative blood loss and ameliorated overall postoperative complications. Loco-regional recurrence rates, overall and recurrence-free survival are similar, furthermore MIT are associated with an undisputable better cosmetic result and this could not be underestimated in a disease frequently affecting young females; however, oncological equivalence of minimally invasive procedures to open surgery still needs to be proved by long-term follow-up data.

Robotic approach (RATS) needs some additional comments, in fact the resection of thymic tumors and thymectomy for myasthenia have been among the first indications in the early 2000s. The 3D visualization, the wristed instrument tips, the precision surgery, dexterity and tremor filtration, the superb view of the anterior mediastinum have progressively made thymectomy one the most appealing thoracic procedure.

Some recent meta-analyses comparing RATS with VATS thymectomy and with open surgery have been recently published [15–17], documenting that in selected stage I/II thymoma cases, RATS thymectomy seems to provide superior results as compared to open surgery, and similar results as compared to VATS. Unfortunately, the limited availability of robotic technology and higher costs still represent a major limitation for the widespread use of RATS.

A rising new technique, largely used especially in Western countries, is the recently proposed minimally invasive subxiphoid approach (3 cm incision made under the xiphoid process and from this access all the instruments are inserted, it can be performed either using video- or robotic-assisted equipment) [18].

According to the proponents of the technique, the subxiphoid approach, by inserting the camera in the midline offers the advantage of a visual field similar to median sternotomy, especially an improved recognition of both phrenic nerves and a secure view field of the neck and vessels. Although promising, the subxiphoid approach is in its very early era, with short follow up and a limited use: so far no definitive conclusions can be made and its efficacy still needs additional confirmation.

Self-study

1. According to current guidelines, which is the indicated surgical approach for thymic pathologies?
   - Sternotomy
   - Transcervical
   - VATS
   - RATS
   - All of these could be indicated according to multiple variables (thymic disease, surgeon experience, local facilities).
2. In case of early stage thymic tumor or thymic hyperplasia associated or not to myasthenia gravis:
   - Sternotomy should be always indicated
   - VATS is contraindicated
   - RATS is the only option
   - minimally-invasive techniques (MIT) including VATS and RATS are nowadays considered standard of care.
3. The main limitation of robotic technology is currently related to:
   - Higher costs, limited availability, need of carefully selection of cases
   - Steep learning curve for surgeons making the technique very complicated
   - High incidence of side effects and questionable result in myasthenia gravis patients
   - Superiority of sternotomy in the vast majority of instances.

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Approaches and Surgical Techniques for Anterior Mediastinal Pathology

Paweł Gwóźdź and Marcin Zieliński

Key Points

- Masses located in the anterior mediastinum vary in histology, malignant potential, treatment and prognosis
- Treatment is guided by cross-sectional imaging and serological markers
- Many masses require core-needle or surgical biopsy
- Surgical approach to resectable lesions depends on their type.

Introduction

The mediastinum is bordered laterally by the pleural cavities, inferiorly by the diaphragm, and superiorly by the thoracic inlet. It is arbitrarily divided into anterior, middle and posterior compartments to help categorise mediastinal diseases according to their location. However, no anatomical planes separate those compartments, and pathological masses may occupy more than one compartment. The anterior mediastinum is bordered anteriorly by the sternum and posteriorly by the anterior surfaces of the pericardium and great vessels. It contains the thymus, lymph nodes, fatty tissue, and, occasionally, ectopic thyroid or parathyroid tissue. All those organs and tissues may give rise to pathological mediastinal lesions, both malignant and benign.

Although anterior mediastinal masses are relatively uncommon, more than half of all mediastinal lesions in adults are located in this mediastinal compartment. The relative frequency of various mediastinal pathologies (shown in Table 1) varies between studies and is dependent on patients' age and sex. However, in the adult population, the most common anterior mediastinal lesions are thymic malignancies followed by lymphomas and substernal goiters.

The majority of anterior mediastinal masses is of primary mediastinal origin, although malignant metastases to local lymph nodes may also occur. Mediastinal lesions are usually asymptomatic and are often discovered incidentally when a chest radiograph or computed tomography (CT) scan is obtained for an unrelated reason. Any symptoms that occur result from the compression or invasion of mediastinal structures adjacent to the tumour. Coughing, chest pain, dyspnea, dysphagia, hoarseness or superior vena cava syndrome (SVCS) may be present. Some lesions may be also associated with generalized symptoms, like thymoma-associated myasthenia gravis (MG), lymphoma-associated B symptoms (chills, fever and weight loss) or gynecomastia accompanying some germ cell tumours (GCTs) with markedly elevated

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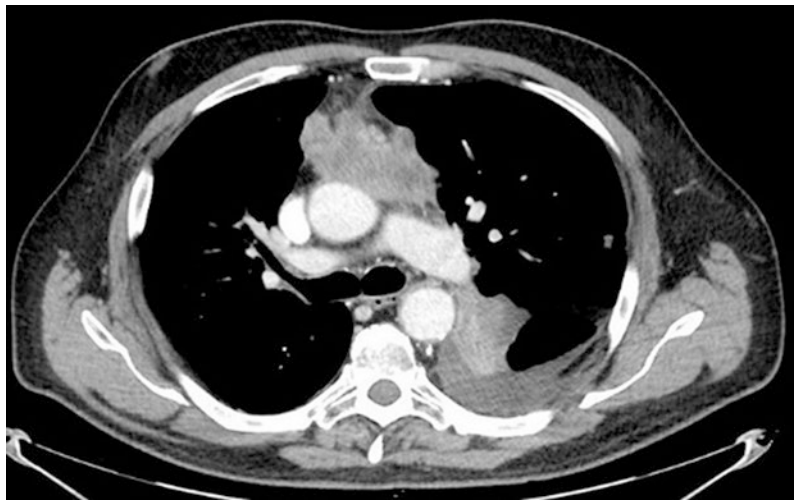

Fig. 1 Stage IV thymic carcinoma in an 60-year old patient. Contrast-enhanced CT showing heterogenous mass in the anterior mediastinum with left pleural effusion and left pleural metastasis

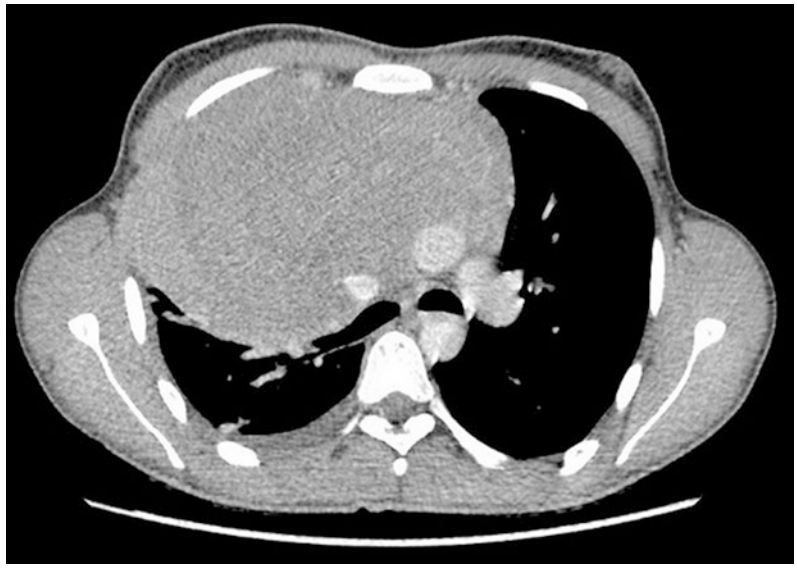

Fig. 2 Hodgkin disease in an 21-year old patient. Contrast-enhanced CT showing homogenous mass in the anterior mediastinum protruding into right hemithorax and compressing right lung

beta-human chorionic gonadotropin (β-hCG) levels. Malignant lesions are more likely to be symptomatic than benign ones. The short time elapsing from the onset of symptoms may be suggestive of highly aggressive tumours such as lymphoblastic lymphomas or non-seminomatous GCTs (NSGCTs).

Diagnostic work-up. The most common initial imaging method used for investigating a suspected mediastinal mass is a chest radiograph. Posteroanterior and lateral chest radiographs can provide information regarding the location, size, composition and density of the lesion. Large lesions may present as soft-tissue masses with

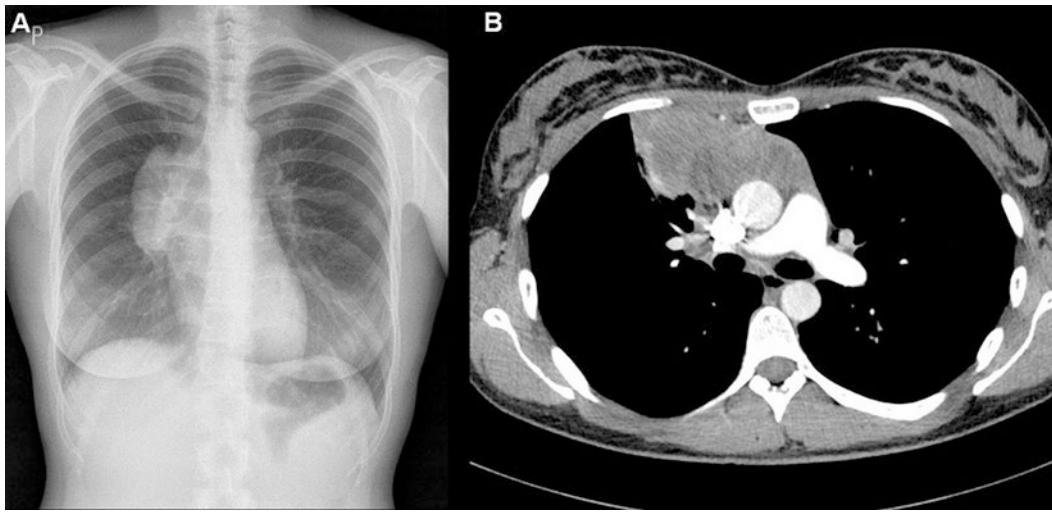

Fig. 3 Primary mediastinal B-cell lymphoma in an 31-year old patient. **a** Plain radiograph showing widening of the mediastinum. **b** Contrast-enhanced CT showing nonifiltrating, homogenous mass in the anterior mediastinum

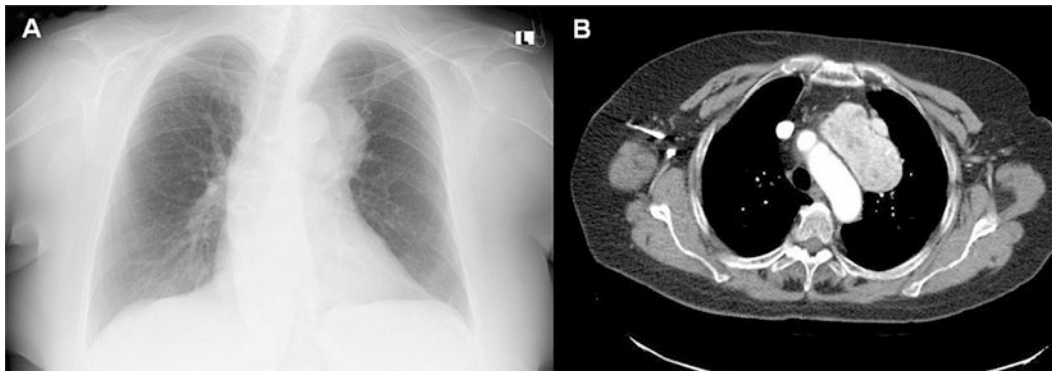

Fig. 4 Substernal goiter in an 72-year old patient. **a** Plain radiograph showing widening of the mediastinum and tracheal deviation. **b** Contrast-enhanced CT showing heterogenous, enhancing mass adjacant to aortic arch

a lack of normal mediastinal contours. Tracheal deviation or pleural effusion may also be present. However, small mediastinal lesions may present subtle radiological signs or may not be visible on chest radiographs at all. In every case, further diagnostic evaluation of the mediastinal mass with cross-sectional imaging like CT or magnetic resonance (MRI) is mandatory. Cross-sectional imaging is a key examination tool used to characterize the lesion, formulate a presumptive diagnosis and guide further treatment. Contrast-enhanced multidetector CT is the imaging modality of choice. It allows for a detailed morphological description of the lesion and assessment of the lesion's size, location and relation to the surrounding structures. An intravenous contrast study allows the involvement of great mediastinal blood vessels by the mass to be assessed. Although MRI does not require iodine contrast administration, it is inferior to CT in imaging most anterior mediastinal pathologies due to poorer spatial resolution. However, MRI is the most useful imaging modality for distinguishing cystic from solid lesions, as in the case of cystic lesions with dense contents that appear on CT images as solid masses. Also, when the CT image is inconclusive, thymic hyperplasia may be differentiated from thymic

Table 1 Anterior mediastinal lesions

Thymic malignancies (thymomas, thymic carcinoma, neurogenic tumours)
Lymphomas (Hodgkin lymphomas, primary mediastinal B-cell lymphomas, lymphoblastic lymphomas)
Substernal goiters
Germ cell tumours (teratomas, seminomas, non-seminomatous germ cell tumours)
Benign thymic lesions (thymic cysts, hyperplasia, thymolipomas)
Metastatic lymph nodes
Parathyroid adenomas
Mesenchymal tumours (lipomas, liposarcomas)

malignancies with chemical shift MRI techniques. A positron emission tomography (PET) scan has little role in the diagnostic work-up of anterior mediastinal lesions. This imaging modality is used to rule out distant metastases if disseminated disease is suspected. It is also used to stage and evaluate the response to treatment of lymphomas.

Serum marker assays play a significant role in the diagnostic work–up of anterior mediastinal masses. Assessment of the serum levels of β-hCG and α-fetoprotein (AFP) is highly useful in the differential diagnosis of GCTs. 70% of patients with NSGCTs have elevated AFP, and 30% have significantly elevated β-hCG. These tumour markers should be obtained in every young male patient with an anterior mediastinal mass, as elevated AFP levels are diagnostic for NSGCTs and the patient can proceed to upfront chemotherapy without the need for tissue confirmation. Serum *lactate dehydrogenase* (LDH) may be elevated in patients with some rapidly growing lymphomas and GCTs. The presence of the antiacetylcholine receptor antibody in a patient with symptoms of MG and an anterior mediastinal tumour virtually confirms the diagnosis of thymoma. Rare neuroendocrine tumours of the thymus may secrete corticotropin-releasing hormone. Substernal goiters may be associated with thyrotoxicosis and mediastinal ectopic parathyroid adenomas are occasional causes of hyperparathyroidism.

When a presumptive diagnosis of an anterior mediastinal tumour can be reliably made on the basis of radiological features and serum markers and the tumour seems to be resectable, the patient may proceed to upfront surgery and tissue biopsy is unnecessary. This is true for lesions like early-stage thymomas, substernal goiters, thymolipomas, teratomas or thymic cysts. Tissue diagnosis is required when the lesion cannot be diagnosed by other means, when upfront curative surgery cannot be undertaken due to local invasion, or when the lesion is to be treated non-surgically. Available techniques for the biopsy of anterior mediastinal lesions include non-surgical transthoracic biopsies (fine-needle aspiration—FNA—and core-needle biopsy) or surgical biopsies by mediastinotomy, video-assisted thoracic surgery (VATS) or mediastinoscopy. Non-surgical biopsies are less invasive and are performed with local anaesthesia. FNA is the least invasive and simplest biopsy method which allows benign and malignant conditions to be distinguished and carcinoma to be diagnosed. However, it has poor accuracy for diagnosing thymic malignancies and diagnosing and subtyping lymphomas, meaning its role in the work-up of anterior mediastinal masses is limited.

Definitive diagnosis of most mediastinal lesions requires core biopsy or open surgical biopsy. A CT-guided percutaneous core-needle biopsy provides a larger volume of tissue sample than FNA with preserved microarchitecture and allows all mediastinal masses to be diagnosed. However, although a less invasive method, its diagnostic accuracy is still inferior to surgical biopsy. The results of core-needle biopsies are often not conclusive and cause unnecessary delay in diagnosis and treatment of rapidly growing mediastinal masses. Surgical

biopsy is the gold standard for the biopsy of anterior mediastinal lesions because the large tissue specimens necessary for diagnosis can be selectively obtained. Surgical biopsy, however, requires general anaesthesia and is a more invasive procedure. The most commonly employed biopsy technique is anterior mediastinotomy (Chamberlain procedure), where a 3–4 cm incision is made over the second or third costal cartilage and the anterior mediastinum is entered through the bed of excised cartilage lateral to the internal mammary vessels. The Chamberlain procedure may also be used for the biopsy of aortopulmonary window lymph nodes (LN), usually during the staging of non-small cell lung cancer (NSCLC). Another approach is VATS, which provides good exposure of the anterior mediastinum and allows for precise dissection of the anterior mediastinum. However, it requires general anaesthesia, single lung ventilation and postprocedural chest drainage. Cervical mediastinoscopy may also be employed for tissue biopsies, although visualisation of the anterior mediastinum is difficult with this technique. This approach is suitable for lesions extending to the visceral mediastinal compartment or those associated with paratrachael or subcarinal lymphadenopathy. Mediastinoscopy is associated with less postoperative pain than both mediastinotomy and VATS. When mediastinal pathology is accompanied by peripheral lymphadenopathy, as is the case for some lymphomas, it is far more convenient to biopsy the easily accessible LN than the mediastinal mass.

Surgical treatment. There is no established standard surgical technique for the resection of anterior mediastinal tumours. For early stage thymomas, a standard thymectomy using a minimally invasive approach (transcervical, VATS, subxiphoid or robotic) is usually conducted. Minimally invasive techniques may also be used for thymic cysts or other small, non-invading mediastinal lesions. For larger or invading tumours, the standard approach is median sternotomy, which provides excellent exposure of the anterior mediastinum. Some tumours that extend into the hemithorax are best approached by a lateral thoracotomy or hemiclamshell incision, especially when the pulmonary hilum is invaded. Large masses that involve both hilums are best approached through a clamshell incision. When the mass is located near the thoracic inlet, an upper sternotomy or neck collar incision may be the most convenient approach.

The goal of surgery is complete resection of the lesion, including metastatic foci. Whenever possible, tumour-free surgical margins should be obtained. If the tumour is invasive, en-bloc removal of all affected structures should be conducted. However, care must be taken to preserve non-involved vital structures, like phrenic and recurrent nerves or great veins. In the case of lung infiltration, wedge resection of involved lung parenchyma is usually sufficient. In more advanced cases, anatomical resections, including pneumonectomy, may be performed if complete resection will be accomplished and the patient has adequate pulmonary reserve. The resection of the invaded or adhering pericardium is always conducted, sometimes with a patch reconstruction. The superior caval vein (SVC) or an innominate vein should be resected only if this is required in order to achieve complete resection. If only one innominate vein is affected, it can be resected without reconstruction. Focal involvement of SVC requires its partial resection with simple suturing or a patch reconstruction using autologous pericardium. For more advanced involvement of SVC or both innominate veins, complete resection and vessel reconstruction using vascular prosthesis (PTFE, bovine pericardial conduit or saphenous vein conduit) is necessary. If a single phrenic nerve is invaded by a malignancy and curative resection can be otherwise performed, it should be resected, if a patient's pulmonary reserve is sufficient. However, both phrenic nerves should never be resected. Instead, the tumour is skeletonized off the nerves. A decision to resect the phrenic nerve in severely myasthenic patients must be carefully judged, as loss of a hemidiaphragm function may be detrimental. Parietal pleural or pericardial implants should be widely resected. Diaphragmatic pleural implants are best removed by full-thickness excision of the involved diaphragm. Some patients may require

extrapleural pneumonectomy for complete clearance of pleural metastases. Some tumours, like malignant thymic tumours, require also regional lymphadenectomy.

In the sections below, a more detailed description of the most common anterior mediastinal masses is presented.

Thymic Malignancies

Thymic epithelial malignancies are the most frequent anterior mediastinal tumours. Thymomas are by far the most prevalent subtype, while thymic carcinomas and neuroendocrine tumours are less frequent. Thymic tumours have no gender predilection, and may occur in any age with peak incidence in the fourth to sixth decade of life. More than half of patients with thymomas are asymptomatic, and one-third present with autoimmune disorders, mainly MG, but also pure red cell aplasia or hypogammaglobulinemia. Patients with larger thymomas or with thymic carcinomas may present with compression symptoms. On a CT scan, a thymoma usually forms a solid, spherical or ovoid, homogenous or slightly heterogenous mass in the anterior mediastinum. Pleural or pericardial effusions may be present, but lymphadenopathy is typically absent. When the mass is infiltrating, large, heterogenous and with lymphadenopathy or distant metastases, a thymic carcinoma or thymic carcinoid should be suspected (Fig. 1).

The resectability of the tumour is the main factor influencing treatment. If the diagnosis of a thymic tumour is highly probable on the basis of cross-sectional imaging and radical surgical resection is achievable, the patient proceeds to curative surgery without the need for a biopsy. Biopsy should be performed in the case of unequivocal CT results suggesting a lymphoma, or in the case of unresectable tumours, before induction chemotherapy or definitive chemoradiation. Tissue may be sampled using percutaneous core-needle biopsy or incisional surgical biopsy through mediastinotomy or VATS. FNA is not recommended. Further information concerning the treatment of thymic malignancies is presented in chapter "Approaches and surgical techniques in the thymus pathology".

Lymphomas

Lymphomas are a diverse group of neoplastic diseases originating from lymphocytes or their progenitors. The most widely used classification system is the World Health Organization (WHO) classification. Primary mediastinal lymphomas originating from lymphoid tissue of the thymus or mediastinal LNs constitute around 25% of anterior mediastinal masses. The mediastinum is also often a metastatic site for a disseminated lymphoma originating elsewhere. Most primary lymphomas are located in the anterior mediastinum, but involvement of the middle mediastinal compartment may occasionally occur. The most common primary mediastinal lymphoma, representing more than half of all cases, is Hodgkin lymphoma (HL). Mediastinal non-Hodgkin lymphomas (NHL) have a more aggressive clinical course than HL and are represented in the adult population mostly by primary mediastinal large B-cell lymphomas (PMLBL).

All mediastinal lymphomas are treated non-surgically. Even when a diagnosis of lymphoma is highly probable on the basis of clinical and radiological features, tissue sampling for histopathological diagnosis and subtyping is mandatory to guide management. Most primary mediastinal lymphomas require tissue samples of adequate size obtained from surgical biopsy. Diagnosis and subtyping of a lymphoma is the most common indication for a mediastinal surgical biopsy. An excisional biopsy of easily accessible metastatic peripheral LN is sufficient for diagnosis and subtyping a primary mediastinal lymphoma and makes mediastinal biopsy unnecessary, thus it is important to assess the status of extrathoracic LNs in every patient with a mediastinal mass. When mediastinal biopsy has to be carried out, the usual approach is anterior mediastinotomy or VATS. Lymphomas extending into the visceral mediastinum or that involve subcarinal or paratracheal LNs may be biopsied through cervical mediastinoscopy. Staging is

done clinically according to the Ann Arbor classification using PET/CT.

Hodgkin lymphoma is a monoclonal B-cell lymphoid neoplasm characterized by the presence of Reed-Sternberg cells. The main HL subtype involving the mediastinum is nodular sclerosis classical HL. It occurs mostly in patients in their twenties and thirties, with slight female predominance. Mediastinal HL usually arises from mediastinal LNs, but may also originate from the thymus. HL spreads to contiguous LN groups, with frequent involvement of hilar, lower cervical and supraclavicular LNs. Typical clinical presentation is a nontender cervical lymphadenopathy. In one-third of patients, general B symptoms are present. Compression symptoms are rare. Other less common symptoms include pain of enlarged LNs after alcohol ingestion, Pel-Epstein fever (intermittent intervals of fever every few weeks) or generalized pruritus. On CT examination, HL presents as mildly-enhancing, homogenous, lobulated soft tissue mass or a group of enlarged LNs in the anterior mediastinum, often with neck or axillary lymphadenopathy. The mass often encircles the great vessels without infiltrating them, a feature that distinguishes HL from other mediastinal tumours. Lung metastases are typically absent (Fig. 2).

Tissue sampling is necessary before initiating treatment. Diagnosis is based on the identification of Reed-Sternberg cells or its variants in the inflammatory environment. As Reed-Sternberg cells are relatively rare in the background lymphoid reaction and mediastinal lymphomas are often fibrotic, large tissue samples have to be obtained during surgical biopsy. The mainstay of HL treatment is chemotherapy, with the optional addition of radiotherapy or stem cell replacement.

Primary mediastinal large B-cell lymphoma is an aggressive lymphoma originating from thymic B cells. It is seen mainly in young adults in their twenties and thirties, with slight female predominance. It is a rapidly growing tumour, usually presenting with compression symptoms like chest pain, dyspnea or coughing, developing over weeks to months. SVCS and pleural or pericardial effusions are common. B symptoms may also occur. Serum LDH is often elevated.

On a CT scan, PMLBL is a homogenous soft tissue mass localized in the thymic area, with frequent lung infiltration. It may contain heterogenous areas of necrosis or haemorrhage (Fig. 3). Although mediastinal, supraclavicular or cervical LNs may be involved, distant lymphadenopathy is uncommon. Dissemination to distant extranodal sites occurs in advanced cases. Diagnosis requires sizeable tissue samples obtained from surgical biopsy due to prominent tissue sclerosis. The mainstay of treatment is chemotherapy and immunotherapy, with the addition of radiotherapy and autologous bone marrow BM transplantation in selected cases.

Lymphoblastic lymphoma is a very aggressive lymphoma usually originating from T cells, although B-cell origin is also possible. Morphologically, a lymphoblastic lymphoma is indistinguishable from acute lymphoblastic leukemia and leukemia is arbitrary defined as a disease with prominent bone marrow involvement. Lymphoblastic lymphomas affect mostly males in the second decade of life, but may occur at any age in both sexes. Usually, the disease is not confined to the chest and also involves extrathoracic lymph nodes, bone marrow or blood. A typical patient presents with enlargement of peripheral lymph nodes, B symptoms and acute compression symptoms due to the rapidly growing mediastinal mass. Symptoms develop acutely over the course of days to weeks. Life-threatening presentations like tracheal compression with stridor, SVCS or cardiac tamponade may occur. Pleural or pericardial effusions are often present and serum LDH level is markedly elevated. On a CT scan, lymphoblastic lymphoma presents as a bulky, heterogenous mediastinal mass that typically involves the thymus with frequent mediastinal lymphadenopathy. As lymphoblastic lymphomas have unique cytologic features, they can be diagnosed using samples obtained by FNA of peripheral LNs, bone marrow biopsies or thoracentesis, making mediastinal biopsies usually unnecessary for diagnosis. Treatment is based on chemotherapy,

with the optional addition of radiotherapy or bone marrow transplantation.

Other lymphomas presenting as mediastinal masses, like mediastinal gray-zone lymphomas, thymic extranodal marginal zone lymphomas of the mucosa-associated lymphoid tissue or anaplastic large cell lymphomas are rare and will not be covered in this chapter.

Endocrine Lesions

Substernal goiter is an extension of the thyroid below the plane of the upper thoracic inlet in a patient in supine position. A goiter grows slowly over many years, extending along the fascial planes usually into the anterior mediastinum, although extension into the medium or posterior mediastinum also occurs. A substernal goiter may be classified as primary, arising from ectopic mediastinal thyroid tissue and with no anatomical continuity with the cervical thyroid, or secondary, which is a mediastinal extension of a cervical goiter. Primary substernal goiters are rare (1–2% of all substernal goiters) and are vascularized by mediastinal vessels (tributaries from internal mammary artery, aorta or other thoracic vessels, depending on localization). Secondary substernal goiters retain thyroid vascularization from superior and inferior thyroid arteries. A substernal goiter is usually discovered in patients in their fifties or older, as goiters grow slowly and takes years to grow large enough to produce symptoms. In the vast majority of patients, iodine deficiency is the main etiologic factor. The spectrum of clinical presentation is broad and ranges from a complete lack of symptoms to acute respiratory failure. The most common clinical presentation is exertional or positional dyspnea resulting from compression of the trachea, occurring in 60% of patients. Other symptoms include coughing, dysphagia, stridor, dysphonia or, rarely, SVCS. When symptoms develop rapidly, they may indicate thyroid cancer, which can be found in up to 10% of patients with substernal goiters.

In all patients, goiters should be evaluated by ultrasonography (USG) and contrast-enhanced CT. All suspected nodules revealed on USG should undergo FNA biopsy, following the guidelines for the treatment of a normal-sized thyroid. On a CT scan, a substernal goiter is a heterogenous (with regions of low attenuation representing cystic changes), hyperdense mass, enhanced after contrast administration (Fig. 4). Continuity with the cervical thyroid is diagnostic for secondary substernal goiters. A biopsy is not necessary to make a diagnosis. In the case of a thyroid carcinoma, loss of distinct mediastinal fascial planes or cervical lymphadenopathy may be present.

The laboratory work-up of substernal goiters includes thyroid function tests, as the disease may be associated with thyrotoxicosis. Iodine-131 scintigraphy should be performed if thyroid-stimulating hormone (TSH) levels are below normal. All patients with substernal goiters causing symptoms should undergo a thyroidectomy. An asymptomatic retrosternal goiter is an indication for surgery only in relatively younger patients, who have a high risk of developing symptoms or malignancy over the years. The vast majority of substernal goiters can be resected through standard cervical collar incision. In rare cases, manubrial transection, sternotomy or thoracotomy is necessary, mainly in cases of ectopic goiters, goiters localized in the medium or posterior mediastinum or extremely large goiters. Complications after thyroidectomies for substernal goiters are more common than after regular thyroidectomies, with enhanced risk for recurrent laryngeal nerve injury, intraopertative bleeding and postoperative hypoparathyroidism. Large substernal goiters with tracheal compression are associated with a risk of transient postoperative tracheomalacia.

Mediastinal ectopic parathyroid adenomas are rare causes of hyperparathyroidism requiring surgical exploration of the mediastinum. The mediastinal localization of parathyroid tissue is a result of their abnormal migration during embryogenesis. These lesions are usually small and require careful preoperative work-up using scintigraphy (technetium-99 sestamibi single-photon emission computed tomography)

fused with CT or MRI, as an intraoperative search for an ectopic parathyroid adenoma is time-consuming and often ineffective. A mediastinal ectopic parathyroid located above the brachiocephalic vein can be approached using a cervical collar incision. Although the traditional approach for lesions located lower in the mediastinum was median sternotomy or lateral thoracotomy, nowadays, after precise preoperative localization with imaging techniques, they can be successfully excised using minimally invasive techniques like VATS, mediastinoscopy or robotic procedures.

Germ Cell Tumours

Mediastinal GCTs are a group of neoplasms arising from ectopic primordial germ cells that were displaced during midline migration in early embryogenesis. GCTs represent 10–15% of all anterior mediastinal tumours, with the mediastinum being the most common site of extragonadal GCTs. GCTs are divided into subtypes that have different malignant potential, prognosis and treatment. Two thirds of GCTs are benign teratomas, for which surgical resection alone is curative. Half of the remaining GCTs are malignant seminomas presenting with good prognosis after chemotherapy. The remaining NSGCTs are highly malignant and have the worst prognosis of all GCTs. In the case of those tumours, treatment is based on primary chemotherapy followed by surgical resection of any residual mass. Although mediastinal metastases of primary testicular GCTs are very rare (especially in the absence of retroperitoneal LNs metastases), in every patient with an anterior mediastinal mass, testicular GCTs must be excluded by physical examination or ultrasound.

Teratoma is a benign GCT that consists of somatic tissue derived from two or three germ layers (ectoderm, endoderm or mesoderm). It may be either mature (composed exclusively of mature tissues) or immature, composed partially or totally from embryonic or foetal tissues and potentially malignant. Teratomas may contain virtually any histologic type of tissue and commonly contain skin and cutaneous appendages, bronchial and gastrointestinal mucosa, pancreatic and neural tissue, smooth muscle and fat. Less frequently, skeletal muscle, cartilage or bone may be present within the lesion. Teratomas typically arise in the anterior mediastinum and often protrude to one hemithorax, but may also be occasionally seen in the posterior mediastinum. Both sexes are affected with equal frequency, and the peak of incidence is between the second and forth decade of life.

Teratomas are usually asymptomatic, slow-growing tumours detected during imaging studies for an unrelated condition. They can grow large and cause compression symptoms (pain, dyspnea, coughing, dysphagia) or lung atelectasis. In rare cases, teratomas may rupture into adhering structures, causing pleural effusion, cardiac tamponade or lung abscesses. When a teratoma erodes into the tracheobronchial tree, the patient coughs up hair (trichoptysis) or sebum. Teratomas may also fistulize to the skin, presenting as sinus drainage. As they frequently contain pancreatic tissue, episodes of hypoglycemia due to hyperinsulinism may be present. Serum tumour markers are not elevated.

On a CT scan, teratomas are large (often exceeding 10 cm), heterogenous, multilocular cystic masses with a combination of coexisting densities of fat, soft tissue, fluid and areas of calcification. Sometimes, bone and tooth-like elements may be identified. Diagnosis is based on imaging studies and does not require biopsy before the initiation of surgical treatment.

As teratomas might complicate and may be potentially malignant, they should always be completely excised, even in asymptomatic patients. The usual approach is by sternotomy or thoracotomy. Occasionally, en-bloc removal of adjacent structures (mainly the lung) is required due to strong adhesions. Due to the large size, adhesions to neighbouring structures and serious consequences of intraoperative rupture of the lesion, VATS approach is limited to small and non-adhering tumours.

Mediastinal seminoma is a malignant neoplasm composed of cells resembling primordial germ cells. It occurs almost exclusively in

young men, with peak incidence in their thirties. Many patients remain asymptomatic at the time of diagnosis. When symptoms occur, they are results of compression, with chest pain and dyspnea being the most common complaints. Seminomas do not tend to invade local chest structures, but around 40% of patients have distant metastases at the time of diagnosis, with lungs being the most common metastatic site. Metastasis to regional LNs is uncommon.

On CT examination, pure seminomas manifest as large, lobular, homogenous soft-tissue masses located in the anterior mediastinum, indistinguishable from lymphomas. However, lung metastases, relatively often accompanying seminomas, are highly unusual in lymphomas. In pure seminomas, AFP is never elevated, and serum levels of β-hCG are normal or only slightly elevated. LDH serum levels are often elevated. When a mediastinal seminoma is combined with an NSGCT component, which can be diagnosed with serologic markers, it is classified as an NSGCT and managed accordingly. Any elevation of AFP indicates the presence of an NSGCT component, regardless of biopsy. Also, β-hCG above 100 ng/mL is unusual for a pure seminoma and suggests the presence of an NSGCT component as well.

A seminoma requires diagnosis from a tissue biopsy before initiation of treatment. CT-guided transthoracic core biopsy is sufficient in many cases and should be performed first. When biopsy results are inconclusive, the lesion should be biopsied surgically. The treatment of seminomas is based on chemotherapy, with radiotherapy applicable for recurrent or persistent mediastinal masses. Surgical excision plays no role in the treatment of mediastinal seminomas.

Mediastinal NSGCTs include embryonal carcinomas, yolk sac tumours or choriocarcinomas. An NCGCT may consist of an isolated single subtype or, often, be mixed with a different subtype of NGCT, or a teratoma, seminoma or even carcinoma or sarcoma. All those tumours are grouped together because they share a similar biology, clinical course and treatment. Any NSGCT may be additionally accompanied by hematologic malignancies or idiopathic thrombocytopenia. Patients are almost exclusively males, usually in their twenties to mid-thirties.

All NGCTs are rapidly growing tumours, presenting with compression symptoms like chest pain, dyspnea, coughing, SVCS or hoarseness, arising in a time period of days to weeks. Generalized symptoms like fever, chills or weight loss can be present. In patients with a choriocarcinoma component, high β-hCG-secretion manifesting as gynecomastia may be present.

At the time of diagnosis, most patients have distant metastases. On CT scans, NSGCTs are large, heterogeneous masses with central areas of necrosis and haemorrhage, infiltrating surrounding structures, often with lung or liver metastases. Cystic spaces indicate a teratoma component within the lesion. Determining serum tumour markers plays a pivotal role in the diagnostic work-up of NSGCT patients. In 90% of cases, serum AFP or β-hCG is significantly elevated, a finding that is pathognomonic for NSGCTs. LDH may also be elevated. A significant elevation of AFT (>500 ng/mL) or β-hCG (above 100 ng/mL) always indicates the presence of a nonseminomatous component of the tumour, and in these patients chemotherapy should be initiated without delaying to perform tumour biopsy. When serum markers are not elevated, or β-hCG is elevated only slightly, histologic confirmation with transthoracic biopsy is required to initiate treatment. Treatment, usually multimodal, begins with cisplatin-based chemotherapy.

A persistent mediastinal mass after chemotherapy is a common finding. Although on pathological examination, this mass may occasionally be a completely necrotic tumour, more often it is a residual NSGCT, a persistent teratoma or a carcinoma/sarcoma. As salvage chemotherapy is rarely efficient, the remaining tumour should be surgically excised whenever technically feasible. Surgical access depends on the exact location and extension of the mass. Usually sternotomy or lateral thoracotomy is utilized. For larger tumours with hilar involvement, a hemiclamshell or clamshell incision needs

to be used. The aim of the surgery is en-bloc radical resection of any residual mass from the invaded surrounding structures such as the lung, thymus, pericardium or, sometimes, great veins or phrenic nerve. In the case of disseminated disease, a pulmonary *metastasectomy* should also be performed.

Benign Thymic Lesions

Thymic hyperplasia. True thymic hyperplasia is a uniform symmetric enlargement of a normal-shaped, triangular thymus, with preservation of normal histologic architecture. It typically occurs after the resolution of a stressful event such as a burn or injury, but also after chemotherapy, radiotherapy or therapy with corticosteroids. Another form is lymphoid follicular thymic hyperplasia, associated with autoimmune diseases like MG, hyperthyroidism or systemic lupus erythematosus. The normal-shaped thymus is enlarged and the thymic cortex is replaced with multiple lymphoid follicles and germinal centres. Thymic enlargement may also not be uniform, but more nodular and similar to thymomas or other malignancies. Chemical shift MRI with in-phase and out-of-phase gradient-echo sequences helps in differential diagnosis in cases of equivocal CT. Alternatively, a follow-up CT scan may be obtained after three months to allow the size of the thymus to decrease. Unless associated with MG, thymic hyperplasia is not an indication for surgical treatment.

Thymic cysts may be congenital or acquired. Congenital thymic cysts are unilocular and commonly located in the neck or anterior mediastinum extrathymically along the developmental tract of the thymus. They are caused by persistence of the thymopharyngeal duct. Acquired, multilocular thymic cysts are the result of thymic degeneration seen in autoimmune diseases, after medical or surgical treatment of mediastinal lesions (e.g. radiotherapy for HL) or in primary thymic malignancies. Malignancy should always be ruled out, as thymomas, lymphomas and GCTs may have cystic components.

Thymic cysts are usually asymptomatic and discovered incidentally on routine chest radiographs. They can grow large and cause compression symptoms. On cross-sectional imaging they present as unilocular or multilocular thin-walled cystic lesions with clearly defined contours and low-attenuating contents. Occasionally, after an intracystic haemorrhage, they may present as lesions with soft tissue attenuation and can be confused with solid thymic tumours. MRI is conclusive in cases of equivocal CT images. Diagnosis is established on the basis of cross-sectional imaging. Resection should be performed for every symptomatic or growing cyst or when malignancy cannot be firmly ruled out by imaging. The traditional surgical approach is median sternotomy or thoracotomy, but nowadays most thymic cysts are resected using minimally invasive techniques (VATS, subxiphoid or transcervical approach). While a complete local excision is sufficient for simple unilocular cysts, a standard thymectomy is advocated for multilocular cysts.

Thymolipoma is a benign lesion originating from the thymus, composed of both thymic epithelial and adipose tissue, with fat accounting for more than half of the tumour mass. Although slow-growing, it can grow very large before symptoms occur. Most thymolipomas are found in young adults, often during diagnostic work-up for recurrent pulmonary infections. Although thymolipomas do not invade adjacent structures, they often present with compression symptoms, which are sometimes significant when the lesion is large. CT scans show a large anterior mediastinal mass of predominantly fat density with strands of soft tissue density, representing normal thymic tissue. It often extends to one hemithorax. Diagnosis is established by cross-sectional imaging alone and tissue biopsy is unnecessary. Thymolipomas should be resected even in asymptomatic patients to prevent further growth and development of symptoms.

Self-study

Which mediastinal mass is the most common indication to surgical biopsy:

A. Thymoma
B. Lymphoma (correct)
C. NSCGC
D. Substernal goiter.

Elevation of serum AFP level is diagnostic for:

A. Hodgkin disease
B. Seminoma
C. NSGCT (correct)
D. Thymic carcinoma.

Primary treatment of seminoma is:

A. Chemoterapy (correct)
B. Surgical excision
C. Radiotherapy
D. Immunotherapy.

Which mediastinal lesion should be always excised:

A. Substernal goiter
B. Teratoma (correct)
C. Thymic cyst
D. Thymic hyperplasia.

The most useful imaging modality of thymic cysts is:

A. Contrast-enhanced CT
B. PET/CT
C. EBUS (transbronchial ustrasonography)
D. MRI (correct).

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Approaches and Surgical Techniques in the Visceral Mediastinal Pathology

Marcin Zieliński and Pawel Gwozdz

Key Points

- Masses located in the anterior mediastinum vary in histology, malignant potential, treatment and prognosis
- Treatment is guided by cross-sectional imaging and serological markers
- Many masses require core-needle or surgical biopsy
- Surgical approach to resectable lesions depends on their type.

Introduction

The mediastinum is a space confined between both pleural cavities, the sternum and the spine, containing several vitally important organs. Laterally, both sides of the mediastinum are covered with the mediastinal pleura. Caudally, the mediastinum connects with a neck and the conventional border is a Thoracic Outlet composed by the upper borders of both first ribs, the sternal manubrium and the spine. Distally, the border of the mediastinum is the diaphragm. Below, the mediastinum connects with the retroperitoneal space. There are several classifications of the mediastinum. The traditional classification includes four parts—the upper mediastinum, reaching the level of the tracheal bifurcation and the lower mediastinum, with three parts—the anterior, middle and posterior, with borders composed by the anterior and posterior wall of the pericardium.

The most used is the classification proposed by Shields, who distinguished three compartments—the anterior, visceral and paravertebral sulci [1] (Table 1). The anterior mediastinum is localized in front of the heart and the great vessels, the middle (visceral) mediastinum lies behind the anterior mediastinum and in front of the anterior surfaces of the thoracic spine and the posterior mediastinum (paravertebral sulci). In this chapter the visceral compartment is addressed. The visceral compartment contains the heart, the aorta and the other main mediastinal blood vessels, the trachea with the main broinchi, the esophagus, the vagus, the laryngeal recurrent and the phrenic nerves, the upper part of the thoracic duct, the mediastinal lymph nodes and the adipose and connective tissue. In some patients the visceral compartment contains the thyroid and the parathyroids, as well. The classification of the mediastinum allows prediction of the pathologies that are possible due to the localization of the diagnosed lesions. The diseases of the heart and the large vessels are the domain of cardiology and cardiac surgery and are beyond the scope of this chapter. The other pathologies belong are the field of interest of thoracic surgery.

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Pathological structures of the visceral mediastinum include various types of lymphomas, metastatic and inflammatory lymph nodes, enterogenous, pericardial and bronchogenic cysts, ectopic goiter, parathyroid tumors, tumors, diverticulae and achalasia of the esophagus and the tumors of the trachea.

The mediastinal pathologies include benign, malignant, inflammatory and functional diseases.

The pathologies of the anterior mediastinum are described in this chapter.

Diagnostics of the Mediastinal Tumors

Diagnostic tests include imaging studies, biomarkers and invasive studies.

In this chapter invasive diagnostic tests will be described.

1. Transthoracic needle biopsy

A transthoracic needle biopsy can be performed with use of fine needle (cytologic sample) or core-needle (histological sample). In either case a biopsy can be done under fluoroscopy, ultrasound or computer tomography (CT) guidance. Generally, a transthoracic needle biopsy, especially a fine-needle biopsy (FNA) is a safe procedure with a low complications rate. The most frequent complication of FNA is a pneumothorax, which does not necessitate a chest drainage in most of patients. The risk of pneumothorax and a subsequent drainage is higher in case of a core-needle biopsy. The other complications of transthoracic needle biopsy are rare. Concerns about injury of the mediastinal large vessels are not supported by the practical experience. The other rare complications include infection and dissemination of neoplasm in the tract of biopsy.

2. Endoscopy

Bronchoscopy and esophago-gastroscopy allow for biopsy in case of the mediastinal tumors infiltrating the airways or the esophagus or the stomach. Modern endoscopic modalities—Endobronchial Ultrasound (EBUS) and Endoesophageal Ultrasound (EUS) combined with FNA enable visualization of the tumor through the wall of adjacent airway/esophagus and obtaining a cytological or histological biopsy under the ultrasonic guidance [3].

Operative Procedures

Diagnostic operative procedures of the mediastinum include mediastinoscopy (video-mediastinoscopy), anterior mediastinotomy (the Chamberlain procedure), video-mediastinoscopic lymphadenectomy (VAMLA) and Transcervical Extended Mediastinal Lymphadenectomy (TEMLA) [2].

Mediastinoscopy

Mediastinoscopy was introduced by Carlens in 1959. Historically, the main indication for mediastinoscopy was staging of lung cancer. However, this technique might be also very useful in case of the pathologies of the visceral mediastinum. Mediastinoscopy is performed under general anaesthesia. A 2–3 cm transverse incision is made above the sternal notch. Subsequently, the trachea is reached and with further blunt dissection a tunnel is made around the trachea, down to the tracheal bifurcation. The mediastinoscope is inserted into that tunnel and the pathological lesion or the mediastinal lymph nodes are visualized and biopsied. The variant of the classic mediastinoscopy is a video-mediastinoscopy, enabling visualization of the enlarged view of the operative field on a monitor screen. The technique of video-mediastinoscopy is much more reproducible and convenient for teaching trainees than the standard mediastinoscopy. The other variant of the standard mediastinoscopy is so called "extended" mediastinoscopy enabling reaching the aorta-pulmonary window area. This procedure involves blunt dissection between the left innominate vein and the aortic arch to create a tunnel leading in the subaortic area. In case of lung cancer the nodal stations 5 and 6 according to the International Association for the Study of Lung Cancer (IASLC) mediastinal nodal map can be reached with a mediastinoscpe inserted

through this tunnel. In case of standard mediastinoscopy or its variants no chest drainage is not necessary after a procedure.

Anterior Mediastinotomy

This technique was described by Chamberlain in 1966. The parasternal incision is made in the anterior chest wall, parasternally to take biopsies from the anterior mediastinal tumors and the nodes of the paraaortic, the aorta-pulmonary window or the paratracheal regions. Anterior mediastinotomy is performed under general anaesthesia. A transverse or vertical incision is made over the cartilage of the second of third rib, which can be resected with preservation of the perichondrium (to allow for the subsequent re-growth of the cartilage). The endothoracic fascia is divided and the mediastinal pleura is dissected bluntly, without entering of the pleural space. The mediastinal tumor or the lymphnodes are reached and biopsied or removed. There is no need for the mediastinal drainage unless the pleural space is violated. In some patients ligation and division of the internal thoracic vessels is necessary. The variant of the anterior mediastinotomy is a procedure including introduction of a mediastinoscope through the intercostal space without resection of the costal cartilage. Anterior mediastinotomy is one of the important techniques in staging of the aorta-pulmonary window nodes for lung cancer.

Video-Thoracoscopy/Video-Assisted Thoracic Surgery (VATS)

Inspection of the pleural space on the high-resolution video monitors allows for diagnostic and therapeutic procedures of the mediastinum. VATS can be performed under local or general anesthesia in the operating room. In case of general anesthesia double-lumen endobronchial tube is usually used. One minimal thoracic incision (uniportal approach) or several incisions with introduction of intrathoracic ports are utilized for a thoracoscope and videoscopic instruments [4]. VATS is especially valuable technique for the areas difficult to reach with use of mediastinoscopy or anterior mediastinotomy, like the aorta-pulmonary window or paraaortic nodes (mediastinal stations 5 and 6), the paraesophageal and the pulmonary ligament nodes (stations 8 and 9) and tumors of the posterior or lower mediastinum. In regard to staging of lung cancer for the mediastinal nodal stations 5 and 6, left-sided VATS is an alternative for anterior mediastinotomy and extended mediastinoscopy. It must be stressed that VATS allows not only for taking diagnostic biopsies but also for therapeutic resection of pathological lesions. Pleural space should always be drained after VATS.

VAMLA

The technique of Video-Assisted Mediastinoscopic Lymphadenectomy (VAMLA) was introduced by Hurtgen in 2001. VAMLA enables lymphadenectomy (removal of the nodes with a surrounding fatty tissue) in comparison to mediastinoscopy witch provides opportunity to biopsy of the nodes, exclusively. VAMLA is performed under general anesthesia with the use of a two-blades mediastinoscope. Extended blades of this type of mediastinoscope allow for wide approach to the mediastinum. The operative incision and range of accessible mediastinal nodal stations is the same an in the case of mediastinoscopy (the subcarinal nodes and the upper and lower paratracheal nodes on both sides). Lymphadenectomy during VAMLA is performed through the lumen of the mediastinoscope.

Transcervical Entended Mediastinostinal Lymphadenectomy (TEMLA)

Surgical Technique of TEMLA

The operation starts with 5–8 cm collar incision in the neck. The platysma muscle is divided and the anterior jugular veins are exposed, suture-ligated and divided. Visualization and

protection of the laryngeal recurrent nerves bilaterally is a priority.

After visualization of both laryngeal recurrent nerves the sternal manubrium is elevated with sharp one-tooth hook connected to the Zakopane or Zakopane II frame (B. Braun, Aesculap-Chifa, Nowy Tomysl, Poland) to widen the access to the mediastinum.

The subcarinal nodes are dissected first. To enter the subcarinal nodes it is necessary to perform a blunt dissection to create a tunnel along the anterior wall of the trachea until the tracheal bifurcation level is reached to divide the firm fascial layer covering the station 7 nodes anteriorly. Dissection proceeds along the medial walls of both main bronchi for the distance of 4–5 cm. The package containing the station 7 and 8 nodes is dissected from the pulmonary artery and the pericardium covering the left atrium (anteriorly) and the esophagus (posteriorly) and removed en-block.

For removing of the subcarinal and periesophageal nodes (stations 7 and 8), a mediastinoscope is used; we prefer the Linder-Dahan videomediastinoscope (Richard Wolf GmbH, Knittlingen, Germany), equipped with moving blades, which are very useful in retracting the pulmonary artery from the carina during dissection of node station 7, and the left atrium from the esophagus during dissection of node station 8, to a level 5–8 cm below the carina. The mediastinoscope is used for retracting of these structures and visualization only—the removing of lymph nodes is carried out using a standard dissector for open surgery, introduced through the right paratracheal space along the mediastinoscope. The Linder-Dahan mediastinoscope is also helpful in removal of the most distal lower paratracheal nodes (station 4L). The dissection the left paratracheal nodes proceeds along the left laryngeal recurrent nerve below the level of the tracheal bifurcation. The nerve is dissected from the left wall of the trachea and the left main bronchus with a peanut sponge, while lateral connections of the nerve are preserved to maintain the blood supply to the nerve. In most patients the left upper paratracheal nodes (station 2L) are located medially and in front of the nerve, while the lower paratracheal nodes (station 4L) almost always lie behind the nerve. The lymph nodes 2L and 4L are dissected carefully with avoiding injury of the left laryngeal recurrent nerve.

To dissect the right paratracheal nodes (station 4R) a mediastinoscope must be withdrawned up to the level of the origin of the innominate artery. The Superior Vena Cava must be localized and en-bloc dissection of the middle mediastinal tissue containing the nodes is performed along the vein below the level of the azygos vein with visualization of the right hilar nodes (station 4R), which are removed.

To enter the station 2R this is necessary to dissect along the right vagus nerve, which lies between the right carotid artery and the right jugular vein. The dissection proceeds along the nerve, below the division of the innominate artery. The origin of the right laryngeal recurrent nerve is clearly visible and protected from injury. Dissection proceeds downwards towards the tracheal bifurcation. The whole fatty tissue containing the 2R and 4R nodes lying between the right innominate vein and the right mediastinal pleura (laterally), the ascending aorta and trachea (medially), the back wall of the Superior Vena Cava (anteriorly) and the esophagus and the thoracic spine (posteriorly) and the right main bronchus, the azygos vein and the right pulmonary artery (inferiorly) is removed.

The highest mediastinal nodes (station 1) are located above the upper margin of the left innominate vein and belong to the anterior lymphatic flow from the chest. The fatty tissue containing these nodes is dissected from the right carotid artery and the right innominate veins (laterally, on the right side), from the left carotid artery (laterally, on the left side), then it is dissected from the trachea (posteriorly) and from the left innominate vein (inferiorly). The piece of tissue containing the station 1 nodes is resected en-block along with the upper poles of the thymus gland.

The entrance to the aorta-pulmonary window and station 6 nodes lies between the left innominate vein and the left carotid artery. The first step to reach this area is the division of

the firm layer of the fascial tissue between the innominate artery, the left carotid artery and the left innominate vein. The fascial layer obscures the view of these vessels and after its division the left innominate vein can be retracted anteriorly. After retracting of the vein upwards using a long retractor, the plane is developed at the anterior surface of the aortic arch. With blunt dissection with use of a peanut sponge the fatty tissue containing the station 6 nodes is dissected of the ascending aorta until the left pulmonary artery is reached. The left vagus nerve is a landmark of dissection. To remove the station 5 and 6 nodes we use video-thoracoscope inserted to the aorta-pulmonary window through the transcervical incision. The nodes located above the convexity of the aortic arch and lying in front of the vagus nerve crossing the aortic arch and the Botallo ligament and the paraaortic nodes (station 6). The nodes located below the aortic arch and behind the Botallo ligament and the pulmonary-window nodes (station 5). Left pulmonary artery, the left phrenic nerve and the left superior pulmonary vein are well visible after completion of dissection. In case of opening of the mediastinal pleura there is no need for drainage of the mediastinum. Insertion of the piece of fibrin sponge and hyperinflation of the lungs during closure of the wound is all what is necessary in such patients. The same rule is valid if the mediastinal pleura is opened on the right side.

Stations 3A (prevascular nodes) and station 3P (retrotracheal nodes) are removed in selected patients. Station 3A nodes lie below the left innominate vein, in front of the Superior Vena Cava, medially to the right mediastinal pleura and laterally to the ascending aorta. These nodes are dissected after removal of station 1 nodes. The left innominate vein and the Superior Vena Cava are retracted posteriorly with a peanut sponge and the fatty tissue containing the 3A nodes is dissected from the structures mentioned above. In our experience these nodes are rarely the site of metastasis only in case the right sided tumors.

The retrotracheal nodes (station 3P) are located behind the bifurcation of the trachea. This area is approached in same fashion as the right paratracheal nodes. The tracheal bifurcation is retracted anteriorly, which enable the visualization of the nodes lying in front of the esophagus. The nodes are easily removed, however we never found any metastatic nodes in this station and most often there are no visible nodes in this location at all. During TEMLA all mediastinal lymph nodal stations and the surrounding fatty tissue are removed with exception of the pulmonary ligament, station 9 nodes. The rule of TEMLA is to perform a lymphadenectomy in en-block fashion, with resection of the whole package of the lymphatic tissue without separation of the individual nodes. It is possible to remove all the nodes of station 1 in one piece containing also the upper poles of the thymus. Afterwards, stations 2R and 4R are removed in one piece, the same as station 7 and 8 and the 5 and 6. We remove the nodes of stations 2L and 4L separately because they almost never occur in one piece of tissue.

Generally, most part of TEMLA is an open procedure, with exception of dissection of the subcarinal (station 7), the periesophageal (station 8) nodes and the left lower paratracheal (station 4L) nodes which are dissected in the mediastinoscopy-assisted fashion with aid of Wolf two-blade mediastinoscope. The paraaortic, station 6 and aorta-pulmonary window, station 5 nodes are sometimes dissected with aid of videothoracoscope introduced to the mediastinum through the operative wound.

Treatment of the Mediastinal Tumors

Tumor of the mediastinal necessitate very individual, diverse treatment approach. The treatment of lymphomas, thymomas, germ cell tumors, thyroid intrathoracic tumors and parathyroid tumors is discussed in this chapter.

Surgery is a mainstay of treatment of many of these pathologies.

There are several surgical approaches that can be used to resect mediastinal tumors.

Minimally Invasive Techniques

These techniques include transcervical, video assisted thoracic surgery (VATS) and subxiphoid/subcostal approaches.

Transcervical Approach

The technique of this approach was described above in regard to TEMLA. There are four types of localization of the mediastinal tumors that can be removed with the use of transcervical approach. There are tumors of the superior mediastinum, located above the level of the tracheal bifurcation. These tumors can be further differentiated as anterior, middle and posterior. The other type comprises tumors located in the inferior mediastinum, below the tracheal bifurcation. The transcervical approach can be useful in removal of many of these tumors. Radical surgery can be performed in the encapsulated tumors or in selected patients with limited infiltration out of the capsule. In case of more extensive tumors the transcervical incision is combined with VATS and a subxipoid incision or a classic open approach through sternotomy or thoracotomy is used for complete resection. The size of the tumor is also important. Although, there is no specific size limit for the use of transcervical approach, however, it would be extremely difficult to remove completely the tumors larger than 8–10 cm in diameter, without disruption of the tumor capsule.

The tumors of the superior middle mediastinum include metastatic nodes, ectopic parathyroid glands and mediastinal cysts. Tumors located in the aortopulmonary area also belong to this category.

Tumors of the Superior Middle Mediastinum

The surgical technique of resection of tumors of such localization resembles the removal of the mediastinal right or left paratracheal nodes described in detail in the chapter on TEMLA. In such instances, the "older" type of technique of TEMLA is used, in which the mediastinum is dissected in the downwards direction, in front of the innominate artery (on

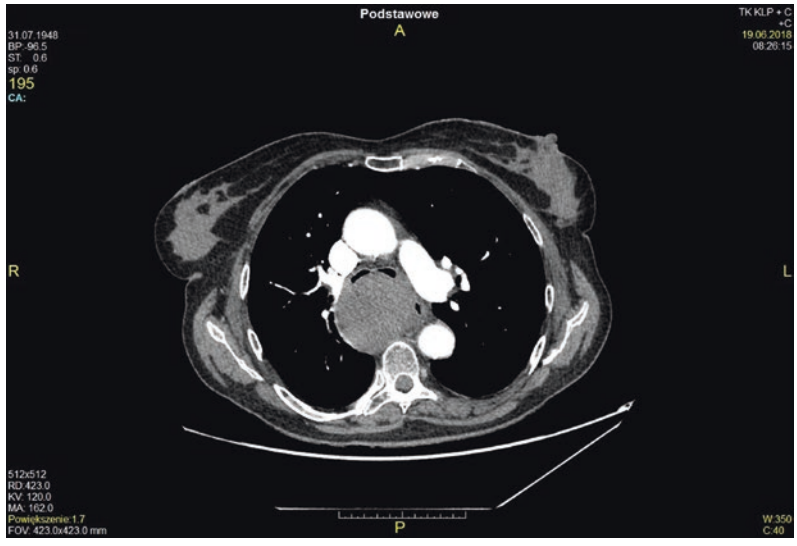

Fig. 1 B-cell lymphoma of the middle mediastinum

Table 1 Typical localization of the mediastinal tumors [5]

Anterior mediastinum	Middle mediastinum	Posterior mediastinum
Thymomas	Enterogenic cysts	Neurilemomas
Germinal tumors	Lymphomas	Neurofibromas
Lymphomas	Coelomic cysts	Malignant Schwannoma Ganglionero-mas
Lymphangiomas	Granulomas	
Haemangiomas	Bronchogenic cysts	Ganglioneuroblastomas
Lipomas	Paragangliomas	Neuroblastomas
Fibromas	Pheochromocytoma	Paragangliomas
Fibrosarcoma	Lymphatic duct cysts	Pheochromocytomas
Thymic cysts		Fibrosarcomas
Parathyroid adenomas		Lymohomas
Ectopic goiter		
Retrosternal goiter		

the right). It is obligatory to clearly visualize all important structures—the trachea, the esophagus, the carotid arteries and the laryngeal recurrent nerves before starting any dissection of the tumor. These structures should be always kept in view during dissection. Cautery or alternative devices should not be used in proximity of the laryngeal recurrent or vagus nerves.

Tumors of the Superior Middle Mediastinum Located in the Aortopulmonary Window Area

The aortopulmonary (AP) window area is entered with use of the technique described in the chapter on TEMLA regarding resection of nodal stations 5 and 6. Thanks to the recently introduced new retractors, a considerably wide access can be created which allows relatively easy dissection of tumors of this location in the semi-open fashion. All anatomical structures of the AP window area are clearly visible which makes any dissection much easier and safer.

There are selected tumors of the lower mediastinum that can be resected through the transcervical approach. These tumors include mediastinal cysts and metastatic nodes positioned close to the esophagus and the bronchi.

VATS

VATS is a widely used approach for biopsy or resection of the mediastinal tumors. There are several variants of VATS including the uniportal and the multipoprtal approaches. VATS is especially important for resection of thomomas, ectopic goiter and the mediastinal parathyroids and the mediastinal cysts, intrathoracic neurogenic tumors.

Subxiphoid/Subcostal Approach

These approaches include the sole subxiphoid with use of VATS technique or the subxiphoid incision might be combined with the transcervical, interocostal, subcostal single or bilateral VATS. The use of CO_2 insufflation or the elevation of the sternum are the options to facilitate an access to the chest.

The main advantage of the subxiphoid approach is an access to both side of the mediastinum through a one incision with clear visualization of both phrenic nerves after opening of the mediastinal pleura on both sides. Generally, a subxiphoid incision is less painful than VATS in the early postoperative period and virtually never leads to the development of a chronic postoperative pain. Subxiphoid/subcostal approach is used predominantly for thymectomy and the other pathologies of the anterior mediastinum.

Open Surgical Approach

These techniques, including partial or complete sternotomy and anterior or posterolateral-thoracotomy were described in detail in this chapter.

In regard to the treatment of the mediastinal tumors it must be stressed that resection of most of the large mediastinal tumors including advanced thymomas and germ cell tumors still necessitate the use of an open approach, instead of minimally invasive techniques.

Tumors of the Middle Mediastinum

Generally, large malignant mediastinal tumors necessitating extensive dissection and resection of the surrounding tissue/organs cannot be resected reliably by the transcervical approach. In selected patients such procedures can be performed with transcervical approach combined with VATS and/or a subxipoid incision. Most of the tumors of the inferior mediastinum cannot be removed with the transcervical technique.

Thyroid Tumors

Intrathoracic thyroid tumors are usually located in the anterior mediastinum and are described in Chap. 48. In rare cases a retrosternal goiter or ectopic goiter can be found in the middle mediastinum. Such patients are relatively easy to diagnose but quite difficult to treat with surgery, which is the prefered therapeutic option in almost all of these patients. In case of a large retrostenal goiter the approach may involve a collar incision in the neck. Elevation of sternal manubrium, as was described for TEMLA may be extremely useful and enables removal of a tumor in most of patients. In extremely difficult cases the use of median sternotomy or thoracotomy is necessary. In case of ectopic goiters possible operative approaches include also VATS.

Lymphomas

Intrathoracic lymphomas may be located in the middle mediastinum, although the anterior mediastinum is more typical for these kind of lesions (Fig. 1). Lymphomas are not described in more detail in this chapter.

Mediastinal Cysts

There benign and malignant cystic lesions of the mediastinum. Cysts of the middle mediastinum are usually bronchogenic, which are the result of developmental disorders.

Beginning from the 4th week of the fetal life the foregut starts to separate from bronchial bud.

Gradually, the airways develop. In 6th week of the fetal life the lobar bronchi develop. Abnormalities of the fetal growth occurring in this period can lead to the development of the bronchogenic cysts, which may be located in the mediastinum or close proximity to the main or lobar bronchi. In 25% of cases bronchogenic cysts can be localized intrapulmonary.

Bronchogenic cysts do not communicate with the bronchial lumen but often are a source of such symptoms as a retrosternal pain, dysfagia, dyspnoe, cough and hemoptysis. Diagnosis is made by use of Chest CT, MRI, EBUS and EUS. Surgery resection of a cyst or part of a lung is a mainstay of the treatment, preferably with use of VATS. Surgical treatment is indicated also in asymptomatic patients due to the risk of possible complications.

Pericardial (coelomic) cysts are most often localized in the right pericardio-phrenic angle, they often communicate with the pericardial cavity. These lesions are usually asymptomatic and are discovered incidentally on a plain chest radiogram. Diagnosis is made based on a Chest CT. These lesions should be operated on only in suspicion of a neoplasm, VATS is a primary surgical technique in these cases.

Lymphatic cysts are rare and may be localized in the proximity of the thoracic duct. A diagnosis is made based on MRI which shows

characteristic attenuation of images. The treatment is a surgical one and involves excision of the cyst and ligation of the thoracic duct.

Self-study

1. What is the posterior border of the middle mediastinum according to the classification of Shields:
   A. Posterior wall of the pericardium (correct)
   B. Sternum
   C. Trachea
   D. Esophagus.
2. Which diagnostic surgical procedures necessitate violation of the mediastinal pleura:
   A. Anterior mediastinotomy
   B. Mediastinoscopy
   C. VAMLA
   D. TEMLA
   E. All
   F. None (correct).
3. Which technique do not allow for biopsy of the aorta-pulmonary window lesions:
   A. Mediastinoscopy (correct)
   B. Anterior mediastinotomy
   C. VATS
   D. TEMLA.
4. Which technique do not allow for entrance to both pleural cavities:
   A. Intercostal VATS
   B. Subxiphoid VATS
   C. Sternotomy
   D. Transcervical incision
   E. None (correct)
   F. All.
5. Which statement is incorrect:
   A. Lymphomas occur more prevalent in anterior mediastinum than in the middle (visceral) mediastinum
   B. Pericardial (coelomic) cysts never communicate with the pericardial cavity (correct)
   C. Bronchogenic cysts are often symptomatic
   D. Coelomic cysts are usually found in the right pericardio-phrenic angle.

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Approaches and Surgical Techniques for Costovertebral Sulcus Pathology

Kyung Soo Kim, Deog Gon Cho, Jae Kil Park, and Seok Whan Moon

The Nervous Vegetative System Pathology

Mediastinal tumors, located in the costovertebral sulcus region, contain neurogenic tumors, cystic lesions of the aerodigestive tract, paravertebral abscesses, meningoceles, and other rare mediastinal tumors [1]. The most common benign neurogenic tumors are schwannomas (neurilemmomas) and neurofibromas, which arise from the sympathetic chain and peripheral nerves. Schwannomas are encapsulated, compressing the nerves and containing Schwann cells with heterogeneous features of fatty degeneration, hemorrhage, and cysts. Neurofibromas demonstrate homogenous, circumscribed but non-encapsulated features, comprised of Schwann cells, nerve fibers, and fibroblasts [2]. Schwannomas are mostly single, but neurofibromas can present with multiple lesions in neurofibromatosis patients. Malignant nerve sheath tumors arise from the peripheral nerves, presenting with aggressive clinical features [3]. Neuroblastomas are the most common neurogenic tumor in children, showing large, lobulated, and encapsulated features in the mediastinum and demonstrating worse prognosis. Ganglioneuromas are smooth, well-encapsulated benign tumors that arise from the sympathetic ganglia, and ganglioneuroblastomas show an intermediate degree of differentiation [4]. Paragangliomas arise from parasympathetic ganglia, and other presenting tumors in the paravertebral compartment include mediastinal teratomas, lipomas, lymphomas, esophageal tumors, lymphangiomas, pheochromocytomas, and angiolipomas.

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Neurogenic Tumors

Introductions

Neurogenic tumors originate from neural crest cells, and nerve sheath tumors are a common pathology in the costovertebral sulcus. Neurogenic tumors represent approximately 9 to 20% of mediastinal neoplasms in adults, and 90% are benign features [5]. The malignancy rate of posterior mediastinal tumors is lower than that of other compartments of the mediastinum,

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but the reported prevalence of malignant posterior mediastinal tumors is higher in children [6]. Posterior mediastinal tumors are mostly asymptomatic and develop as slowly growing lesions that are incidentally found. Invasion of adjacent structures of the vertebrae, ribs and vascular and neurologic systems causes related symptoms. The presenting symptoms are chest pain and respiratory symptoms, such as coughing, dyspnea, and dysphagia. Neurologic manifestations develop due to the compressive effect of the tumor around the nervous system and spinal canal involvement [7]. Surgical resection is the optimal treatment for neurogenic tumors in the posterior mediastinum. Understanding of the anatomy of the neurologic system is important for close dissection. Surgery-related complications include postoperative neuralgia, Horner's syndrome, hoarseness, phrenic nerve injury, and bleeding in vascularized tumors. To decrease morbidity, mass-abutting nerves, adjacent vascular and bony structures, and symptoms of mass effect are important factors for consideration of proper surgical approaches [8].

Preoperative Evaluation

Approaches and surgical extents are varied according to the tumor size, location of the mass, age, and involved adjacent structures, such as vertebral and spinal canal involvement [9]. A simple chest X-ray is the first modality to detect mediastinal tumors in both adults and children. However, small-sized posterior mediastinal masses are not well detectable due to regions obscured by the cardiac, aorta, ribs and vertebral columns. Chest computed tomography (CT) is a standard diagnostic tool to characterize masses for precise evaluation. Magnetic resonance imaging (MRI) is helpful for differential diagnosis and beneficial for evaluating the ranges of tumor invasiveness around the intervertebral foramen and spinal cord [10]. F-18 FDG uptake on PET/CT scan can determine the malignant nature of the tumor or metastatic lesions, guiding treatment planning for multidisciplinary approaches [11].

Surgical Approaches and Techniques

Surgical procedures for neurogenic tumors have been established with evolving advanced instruments and techniques in the decades since the early era of video-assisted thoracoscopic surgery (VATS) [12]. Thoracoscopic resection is safely performed, and potential bleeding in patients with vascularized lesion can be controlled under direct inspection, compared to percutaneous techniques [13]. Adequate excision of the tumor is generally attempted without tissue confirmation [14]. Several studies have demonstrated shorter operating times, fewer complications, less pain and shorter hospital stays with VATS for posterior mediastinal tumors, compared to open surgery [15]. Under general anesthesia with one-lung ventilation, the patient is placed in the lateral decubitus position, and the operating table is flexed to widen the intercostal spaces. The patient can be tilted forward to retract the lungs with gravity and enhance adequate exposure of the tumor in the paravertebral sulcus region. A 5- or 10-mm, 30-degree angled scope is useful for exploration of the entire thoracic cavity, and multi-port (2 or 3) to single port techniques are modifiable, according to the size, location and nature of the tumor. However, the placement of port sites with working incisions should be planned, expecting possible additional ports, risk of bleeding, and pathology retrievals. Instruments and scope ports should be gently manipulated without causing intercostal nerve compression and vessel injury. Meticulous dissection after sharp incision of the capsule around the neurogenic tumor is continued straightforwardly. A small peanut-stick blunt dissector and endo-suckers are useful for facilitating meticulous pleural dissection for enucleation of the tumor. Most of the small neurogenic tumor is well encapsulated and seated without adherence to the costovertebral junction, which is readily removed. Ultrasonic devices and bipolar diathermy are useful for circumferential dissection around the pleura and the tumor bed. Electrocauterization is carefully utilized in close dissection around the sympathetic chain

ganglion, phrenic nerve, and recurrent laryngeal nerve to avoid thermal injury. Gentle grasping of the dissected capsule using thoracoscopic instruments is helpful for retraction and exposure of the tumor bed, to avoid forced traction of the nerve root. Cutting with endoscopic scissors using endoscopic clip ligations is advantageous to divide the feeding vessels or nerves to the tumor, without injuring the neurovascular structures (Fig. 1).

The completely excised specimen is removed using disposable bags or globes through the working incision. Meticulous hemostasis around the tumor bed is facilitated with surgical glue and coverage using cellulous mesh. Local anesthetic agents for intercostal blockade around the intercostal spaces can be applied by intrapleural instillation using needling techniques. A drainage chest tube is placed through the port site under lung expansion with thoracoscopic viewing during wound closure. Most patients are discharged with short hospital stays, confirming neither pneumothorax nor pleural effusion on chest X-rays.

Most posterior mediastinal tumors are managed by VATS as a diagnostic or therapeutic tool without complications or recurrence. However, the approach for conversion to thoracotomy should be considered to attain complete resection of the tumor with negative margins in situations of enormous tumors. Some tumors are highly suspicious for malignancy, or they are ranged into the spinal canal, compressing the spinal cord (dumbbell tumors), and minimally invasive VATS is not proper for treating invasive tumors [16]. These huge, adherent tumors with intraspinal extension require open thoracotomy to achieve complete resection of the tumor [17]. Preoperatively suspected cord-compressing tumors on radiology images are managed by sequential, combined, extensive neuro-thoracic surgery [18]. With the patient in the prone or lateral position to the table, rotating anteriorly, laminectomy is performed by neuro-spine or

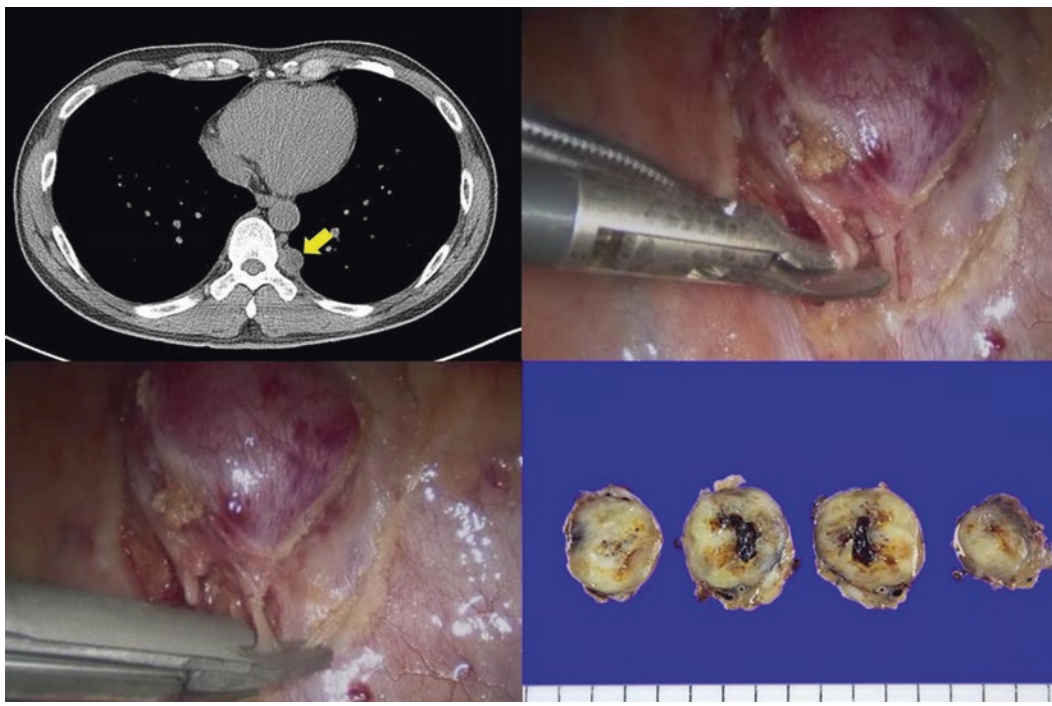

Fig. 1 Video-assisted thoracoscopic view for resection of posterior mediastinal tumor (*yellow arrow*). Thoracoscopic ligation and cutting of the neurovascular stalk after application of surgical clips. The pathology revealed a 2.3 × 1.8 × 1.6 cm-sized schwannoma

orthopedic surgeons, and thoracoscopic or open thoracotomy procedures are followed with the patient in the lateral decubitus position [19]. Leakage of cerebro-spinal fluid, spinal cord damage and compression hematomas in the spinal canal should be cautiously monitored to minimize neurologic sequelae postoperatively [20].

Recently, a single incision VATS approach was adopted with its less invasive purposes, gaining favorable outcomes with low morbidity. A uniportal technique for small-sized neurogenic tumors can be conducted using single intercostal level, not increasing additional nerve injury, compared with multiport technique (Fig. 2).

Robotic surgery has also demonstrated usefulness for treating posterior mediastinal tumors with fine, rotating movement of articulating instruments [21]. A robot-assisted scope view provided magnified, fine 3D visualization of limited surgical fields around the costovertebral sulcus up to thoracic inlet level (Fig. 3). Articulating instruments and robotic arms afford the surgeon the ability to manipulate round neurogenic tumors without instrumental collisions [22].

In summary, complete surgical resection is the standard modality, with a diagnostic and therapeutic role in the treatment of neurogenic tumors in the posterior mediastinum. Variable techniques have been developed with benefits and acceptable outcomes for decades. Thoroughly chosen surgical approaches according to the status of the tumor are important to decrease patient morbidity in the treatment of posterior neurogenic tumors.

Self-study

1. The most common posterior sulcus pathology in adults is:
   (a) Ganglioneuroma
   (b) Neuroblastoma

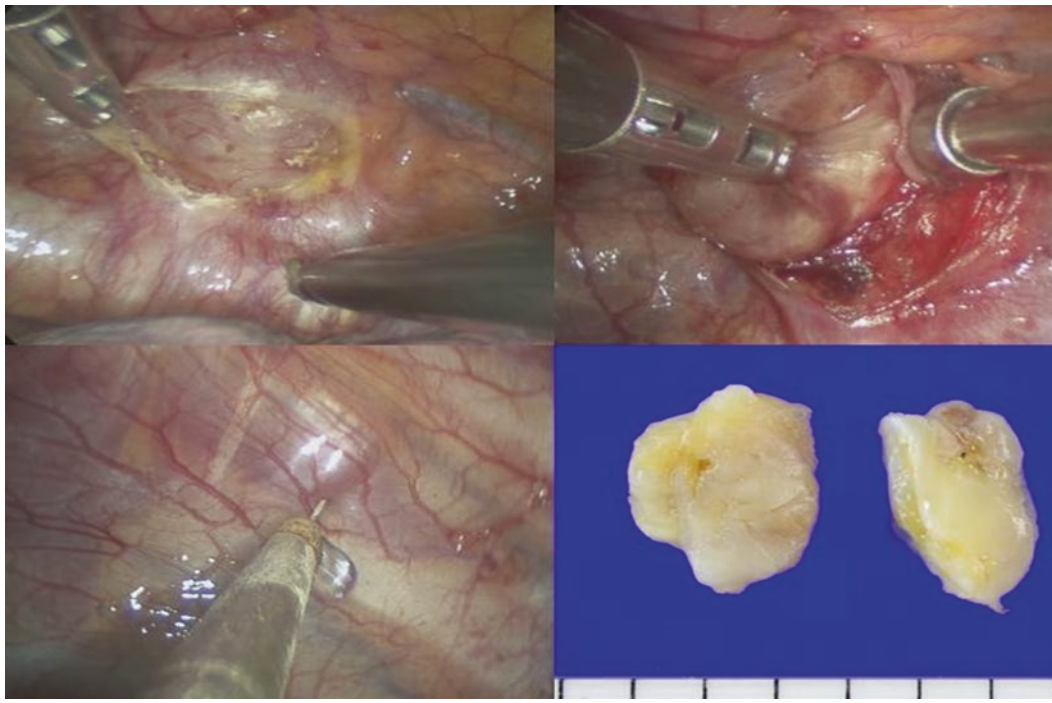

Fig. 2 Well-defined nodular lesion in the right paravertebral region of T2, in the 1st intercostal space, was removed via the uniportal VATS approach. Thoracoscopic intrathoracic intercostal nerve blockage was introduced for postoperative pain control. The pathologic result revealed a pale, brown-colored, 2.3 × 1.8 × 1.6 cm-sized mass, proved to be a schwannoma

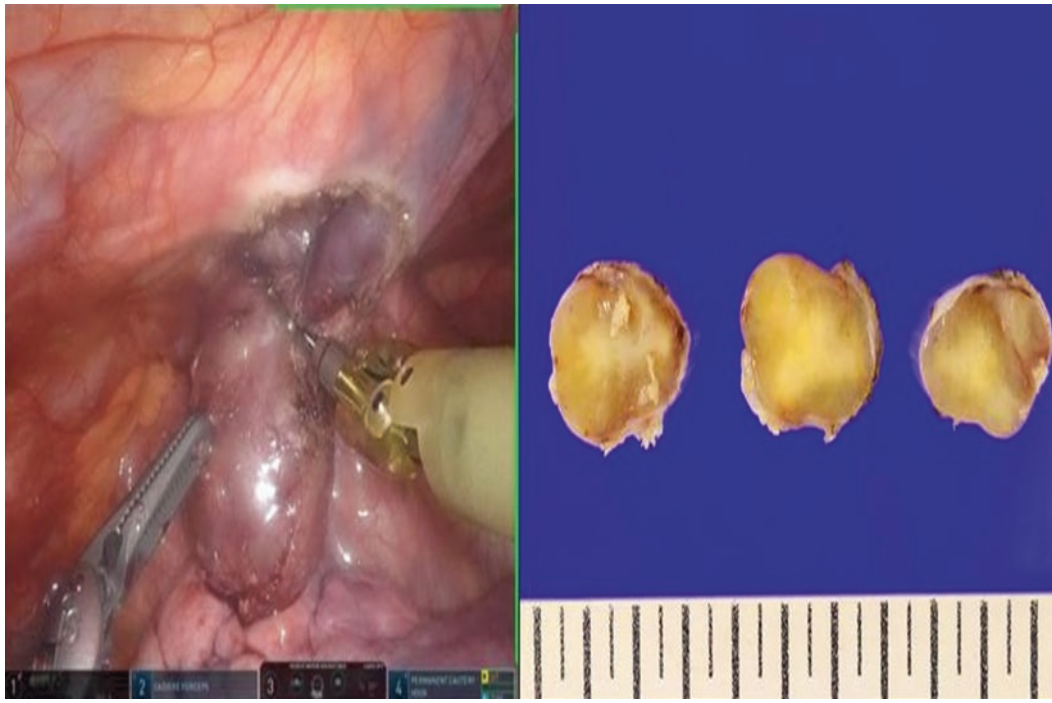

Fig. 3 Rotatable, articulating robotic instruments enhance meticulous dissection of a thoracic inlet tumor at the 1st intercostal level. An irregularly shaped, 1.2 × 1.0 cm-sized, pale brown soft tumor was diagnosed as mediastinal neurofibroma

(c) Schwannoma
(d) Paraganglioma

2. Which statement is incorrect:
   (a) Chest computed tomography (CT) is a standard modality for the preoperative evaluation of mediastinal neurogenic tumors.
   (b) Curative complete resection of posterior sulcus tumors depends on the size, location and invasiveness of the tumor.
   (c) Combined approaches by spinal surgeons might be required for invasive, dumbbell shaped paravertebral tumors.
   (d) Benign neurogenic tumors are always symptomatic and rarely found incidentally.

Answers

1. The most common posterior sulcus pathology in adults is:
   (a) Ganglioneuroma
   (b) Neuroblastoma
   (c) Schwannoma—**CORRECT.**
   (d) Paraganglioma

2. Which statement is incorrect:
   (a) Chest computed tomography (CT) is a standard modality for the preoperative evaluation of mediastinal neurogenic tumors.
   (b) Curative complete resection of posterior sulcus tumors depends on the size, location and invasiveness of the tumor.
   (c) Combined approaches by spinal surgeons might be required for invasive, dumbbell shaped paravertebral tumors.
   (d) Benign neurogenic tumors are always symptomatic and rarely found incidentally. —**INCORRECT.**

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Approaches and Surgical Techniques for Superior Vena Cava Syndrome

Jean Yannis Perentes, Matthieu Zellweger, and Michel Gonzalez

Key Points

- The "Superior vena cava syndrome" (SVC syndrome) results from an obstruction of the blood flow in the SVC. It can develop slowly or acutely as a result of malignant or non-malignant processes.
- Surgical management of SVC syndrome can be considered in situations of locally advanced disease (i.e. Thymoma, NSCLC) in a multimodal therapeutic approach.
- SVC clamping and replacement during surgery should be either limited in time to avoid hemodynamic instability or upper body venous hypertension. An elegant way to overcome this problem is to use bypass methods.
- SVC replacement results are good regarding graft patency.

Introduction

The term "Superior vena cava (SVC) syndrome" describes the signs and symptoms resulting from an obstruction of the SVC. These can take many forms but are all related to an obstruction of the blood flow in the SVC. In most cases, this is due to an external compression of the vessel by a mediastinal or pulmonary mass. On rare occasions, the SVC obstruction can result from the intravascular thrombosis of an intraluminal device, from infections, from the compression of the SVC by an aortic aneurysm or from fibrosing mediastinitis.

The symptoms of SVC obstruction include increased venous pressure in the upper body with development of face, neck and arm edema as well as swelling of the veins located proximally to the venous obstruction. Additional symptoms can include shortness of breath, cough, dysphagia, headaches and high-pitch wheezing. All these symptoms are related to edema of the tracheal bronchial tree and of the larynx. These are rarely life-threatening symptoms with the exception of the very few patients developing cerebral or epiglottis edema.

Anatomy and Pathophysiology

The SVC is the main vessel that transports deoxygenated blood from the systemic circulation of the upper body back to the heart atrium. It is a short (approximately 70 mm on average), large-diameter (>20 mm) vein that it is located on the right side of the upper part of the anterior mediastinum. It usually runs from the lower border of the anterior portion of the first rib and empties into the upper border of the right atrium behind the lower border of the rib.

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The SVC is characterized by a thin vascular wall and low intravascular pressure. It is surrounded by mediastinal lymph nodes, the lungs and more rigid elements such as the sternum and the right main bronchus. These aspects make the SVC rather prone to obstruction due to pathologies of the surrounding structures (mediastinal or pulmonary).

An SVC obstruction can occur over a long period (mass growth with progressive obstruction) or acutely (catheter thrombosis). If the obstruction develops over long periods of time, the venous system progressively adjusts the drainage capacity of collateral veins to find alternative pathways to the heart. These collateral systems have been widely studied and include four major routes: the azygos vein; the internal thoracic veins (iliac veins, epigastric veins, internal thoracic vein, Inferior Vena Cava (IVC)); the vertebral veins (sinus venosus and bilateral brachiocephalic veins, then intercostal, lumbar and sacral veins); and the external thoracic veins (subclavian and axillary veins, then lateral thoracic vein, thoracoepigastric and superficial epigastric veins into the femoral vein) [1, 2].

In case of progressive SVC obstruction, these collateral pathways develop slowly over time and allow the diversion of the venous flow from the SVC back to the heart through them. On the other hand, if obstruction develops acutely, the venous system does not have time to adjust to the SVC obstruction and severe symptoms will occur [1, 2].

Etiology

The SVC syndrome was first described in the eighteenth Century by William Hunter. At the time, it was mainly caused by aneurysms of the ascending aorta resulting from Tuberculosis or Syphilis. Nowadays, its etiology has shifted to reflect the current epidemiology of thoracic diseases, and the vast majority of cases is due to thoracic malignancies (primary or metastatic), mainly bronchogenic carcinomas.

Interestingly, non-malignant causes of SVC syndrome have increased over the past few years from 5 to 40% of all etiologies mainly due to the obstruction of intra-vascular devices such as catheters, pacemaker wires and in-dwelling devices.

Thoracic malignancies remain the major cause of SVC syndrome with more than 60% of all cases. In most patients, the diagnosis of an SVC syndrome is related to an underlying neoplasm.

Malignant Causes

The appearance of SVC syndrome in patients with malignancies depends on the growth characteristics of the malignancy. The most frequent malignant cause of SVC syndrome are lung cancers, although only a small percentage (<5%) of patients with lung cancer eventually develop SVC syndrome. Patients with Small-Cell Lung Cancer (SCLC) account for the higher percentage of cases owing to the growth pattern, localization and lymph node invasion properties of SCLCs. However, the higher overall incidence of NSCLC explains that this latter pathology is a more frequent cause of SVC syndrome.

The second-most common malignant cause of SVC syndrome are mediastinal lesions such as non-Hodgkin's lymphomas or thymoma. Other malignant diseases may also be associated to SVC syndrome including mesothelioma and primary or metastatic mediastinal tumors.

Clinical Evaluation

The clinical symptoms of SVC can vary from mild to severe. The most frequent signs and symptoms are facial swelling (present in > 70% of cases), dyspnea (60%), coughing (40%) and arms swelling (30%). Other signs and symptoms such as those described in the introduction are less frequent. Irrespective of etiology, facial edema and dilated neck and chest veins are the most frequently observed symptoms. It should

be noted that in cases of very slow development of the SVC syndrome, the symptoms might be rather mild, or almost silent and mostly detectable in lying patients where the venous pressure increases significantly [1, 2].

Most patients report an exacerbation of the symptoms when they are lying down or bending forward. More generally, the patients will observe more marked signs and symptoms in the mornings and frequently find some degree of relief when standing up or sleeping upright.

In cases of more acute SVC occlusions, alternative drainage pathways do not have time to develop, and patients are usually symptomatic. Venous patency and presence of thrombotic material must be determined rapidly after the onset of symptoms. Urgent endovascular treatment is then needed with thrombectomy and stent placement. Even in such cases, it should be stressed that SVC syndrome is rarely life-threatening [1, 2].

Pre-operative Assessment

An SVC syndrome is generally not of benign etiology. In most cases, a chest X-ray radiograph may suffice to correctly diagnose an SVC syndrome and its hallmark radiographic features, mediastinal widening and pleural effusion.

A CT scan is the general exam of choice to diagnose the cause of SVC obstruction and to orient additional examinations.

Venographic imaging methods based on Magnetic Resonance techniques may be of help to assess SVC occlusions in patients unfit for CT scan, although some controversies endure as to whether the former method is superior, equal or inferior to CT scan. In the same spirit, some ultrasonographic approaches might add some information on the severity of the SVC occlusion, but are not the choice method for pre-operative assessment [1, 2].

The SVC syndrome can be classified according to its radiological signature [3]:

- Type 1A—Moderate SVC narrowing with no collateral venous flow
- Type 1B—Severe SVC narrowing with retrograde flow in the azygos vein
- Type 2—SVC occlusion above the azygos vein with retrograde flow into thoracic, vertebral or other collateral networks
- Type 3—SVC occlusion below the azygos vein with retrograde flow through the azygos vein into the IVC
- Type 4—SVC occlusion at the azygos vein with multiple small peripheral collateral flows.

In general, pre-operative assessment of SVC syndrome patients should encompass all intrathoracic pathologies/malignancies and a clear evaluation of the patient's lung and cardiac functions to clarify, amongst others, their post-surgery pulmonary function should a lobectomy be indicated [4, 5]. This is particularly acute in patients whose prognosis is poor and in patients with N2 disease [4]. Apart from the characteristics of the SVC syndrome itself (extent, location, severity), the assessment should also study the possible anastomosis sites, the exact anatomy of the venous network of each individual patient, the possible invasions of the SVC by a malignancy and the involvement of the phrenic nerve (bilateral involvement being a contra-indication to surgery) [4].

Diagnosis

The occlusion of the SVC is most often the result of another disease. Treating this underlying condition is the key to managing an SVC syndrome. In most cases, the underlying condition is a malignancy, sometimes as yet undiagnosed. Thus, proper assessment of this malignancy is essential, and should focus on lung lesions (primary or metastatic) and non-Hodgkin's lymphoma, since these are the most frequent malignant causes of SVC syndrome [1, 2].

Multiple approaches are possible to obtain tissue for diagnosis including from distant metastases when present. These approaches include bronchoscopy or surgical interventions

on the anterior mediastinum. This diagnosis is essential for prompt therapeutic intervention either by systemic drugs, surgery or radiation therapy.

Medical Management

The main goal of medical management of SVC syndrome is to alleviate the symptoms to restore the patient's quality of life. In parallel, utmost care should be given to the treatment of the underlying disease. Thus, any course of medical management of SVC syndrome should encompass the constraints and realities of the treatment of the underlying disease as well as the acuteness and severity of SVC syndrome symptoms [1, 2].

In cases of thrombosis due to the use of an intravascular device, removal of the device should be considered, possibly accompanied by anticoagulation, although there is no commonly accepted evidence to demonstrate a clear gain of anticoagulation [2]. Other courses of medical management (diuretics, steroids) are reported, without clear benefit (nor obvious disadvantage) for the group of patients studied [6].

If a given patient with SVC syndrome has a radio-/chemo-sensitive tumor, SVC symptoms might be alleviated by a course of radiotherapy/chemotherapy aimed against the malignancy. It is interesting to note that the resulting decrease in SVC mechanical occlusion and concomitant restoration of blood drainage might be compounded by the alternative venous drainage pathways (which do not necessarily shut off when the SVC occlusion decreases) to produce a more thorough symptomatic relief than would otherwise be expected based on the occlusion relief alone.

Finally, stenting is an option to alleviate the symptoms of SVC syndrome and restore the normal functioning of the SVC. This approach can be useful for fast symptomatic relief, or in patients with radio- or chemo-resistant malignancies. This approach is useful but carries a 4% rate of complications, sometimes severe or even fatal (severe hemorrhage, cardiac events or respiratory failures) [22].

Surgical Management

Surgical management of SVC syndrome is either endovascular or surgical. The first approach is generally performed to alleviate the SVC symptoms before or during the initiation of definitive therapy (chemo-, radio-, immunotherapy) while the second is performed in combination with mass resection and includes SVC reconstruction. Most cases of lung cancer or mediastinal tumors invading the SVC are managed with multimodal therapy.

Usual surgical approaches are thoracotomy at the fourth or fifth intercostal space for lung malignancies, and central sternotomy for malignancies located in the anterior mediastinum. Each technique has advantages and disadvantages in terms of exposing the SVC and allowing the harvest of other venous segments. Further approaches described by some authors [4] include hemi-clamshell thoracotomy, cervico-sternotomy and combined cervico-sternotomy with thoracotomy.

The choice technique for resection and reconstruction of the SVC itself depends on the degree of invasion of the SVC. If the invasion is not complete (<50% of the diameter of the SVC is involved), the SVC can be partially clamped to allow resection of the defect, followed by a primary suture repair or a patch repair [4]. This is not usually associated with any manner of severe hemodynamic imbalance [1]. If the involvement of the SVC is >50% of its diameter, a graft repair is indicated [4], using end-to-end interposition of a prosthetic graft (usually made of Poly-tetrafluoro-ethylene (PTFE)) [7–10] or autologous pericardium or saphenous vein patches shaped into a tube [5, 11–14]. In this latter case, it is necessary to use total SVC clamping to perform the surgical intervention [1]. This intervention must be limited in time, although some authors report that 60 minutes of clamping are acceptable in relevant animal models [4]. Care must be exercised that clamping the SVC above the azygos vein might induce cerebral side-effects (anoxia and ensuing edema).

There are several surgical techniques described for SVC reconstruction using a PTFE prosthesis [1]. The "trunk replacement" aims at inserting a segment of PTFE graft between the innominate veins confluence and the cavo-atrial junction to replace the SVC segment invaded by a malignancy. The "revascularization from the left (or right) innominate vein" connects the innominate vein either directly into the atria or into the lower stump of the SVC. In most situations, the reconstruction of only one side is necessary: innominate or jugular to right atrium (Fig. 1).

Logically enough, patients with a long-standing SVC syndrome and well-developed alternative venous drainage pathways might sustain the SVC clamping with relatively few unwanted effects. On the other hand, patients with more acute occlusions of the SVC will have to be monitored carefully and possibly linked to bypass techniques when the SVC is clamped because it interferes with the upper body venous return [5]. Common side-effects to be aware of are loss of blood volume, decreased cardiac output and hypotension, as well as cerebral thrombosis or edema [5, 15]. All of them can develop into life-threatening conditions and must be managed accordingly [5]. Thus, much care should be taken when considering the timing of SVC surgery on patients presenting acute SVC occlusion [1, 4].

Various methods exist to moderate the effects of SVC clamping and mitigate its potential consequences [5]. These include standard methods such as pharmacological support for blood pressure, cardiopulmonary bypass and temporary innominate-to-atrium bypass [5, 11, 12, 16–18]. Whilst the above-mentioned methods achieve to goal of hemodynamic stabilization, they all have specific limitations, be they in duration or patient eligibility (pharmacological support for blood pressure), exclusion criteria such as being contra-indicated in patients with prior cardiopulmonary insufficiency [5], possible complications including those due to full heparinization [17] or mere practicality [16, 18].

One relatively recent method is a simple jugulo-femoral bypass, driven by the pressure gradient naturally occurring between these two veins [5]. This approach was demonstrated to be not only simple, but safe and efficient in preventing hemodynamic instability during and

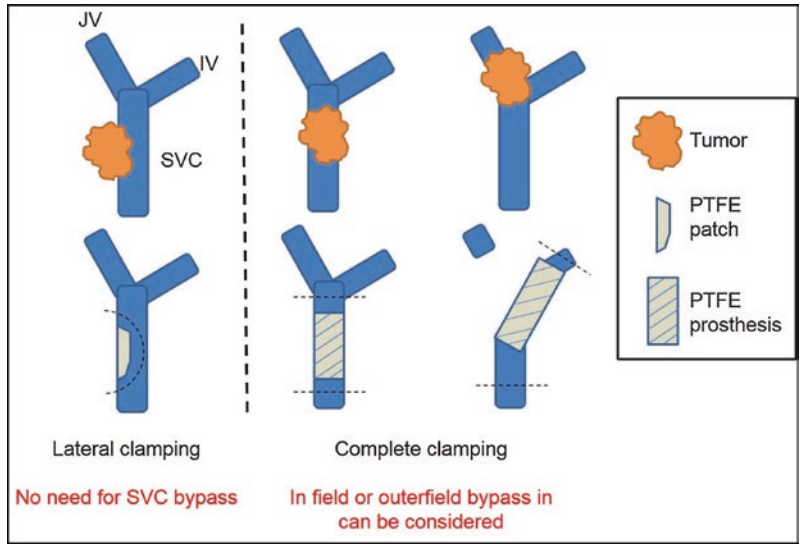

Fig. 1 Various situations of SVC invasion by tumors and corresponding reconstruction approaches. Lateral invasion can generally be managed by partial vein reconstruction using a side clamping technique. In situations of transmural invasion of the SVC, complete clamping and replacement of the vessel is necessary. For this, we recommend a bypass approach to avoid hemodynamic instability. For complete SVC replacement we use armed PTFE prostheses

after SVC clamping, without any need for full dose, systemic heparinization [5]. Furthermore, should the need to clamp the SVC arise intra-operatively, this method can in fact be activated in a very short time, a useful advantage in cases where surgery appears more complex than initially envisioned [5]. The development of mini extra-corporeal circulation devices has also allowed improvement of these approaches by the addition of a pump to the device to ensure up to 3 liters/min of flow between the upper and lower body. This allows SVC clamping for as long as necessary without hemodynamic instability or need for important heparinization (Fig. 2).

The induction of anesthesia in patients with SVC syndrome may not be as straightforward as in other patients. In particular, some authors report that these patients might develop unexpected life-threatening symptoms when anesthesia is induced [16]. In this respect, an additional advantage of the bypass technique described above and in Fig. 2 (left) is that it can be placed and activated before the induction of anesthesia [5, 19].

Most complications observed following SVC surgery are respiratory, including some infections secondary to pulmonary infectious complications [4, 12]. Some authors report rates of post-operative mortality and morbidity as high as 14% and 40%, respectively [4], although careful patient selection might help minimizing such figures [1]. Some thrombotic events are also reported up to six months post-surgery, possibly due to SVC stenosis at the repair site. Some authors indicate, however, that mortality following SVC clamping and surgery might be related to the resection extent, rather than to the SVC clamping or reconstruction [5]. Complications more specifically related to PTFE grafts include stenosis at the site of anastomosis, thrombosis due to insufficient flow through the graft (for instance when the collateral drainage pathways are well developed) and potentially severe infections [1]. It should be borne in mind that it might be difficult to disentangle possible complications arising from the surgical acts themselves from those arising from hemodynamic instability during the operation.

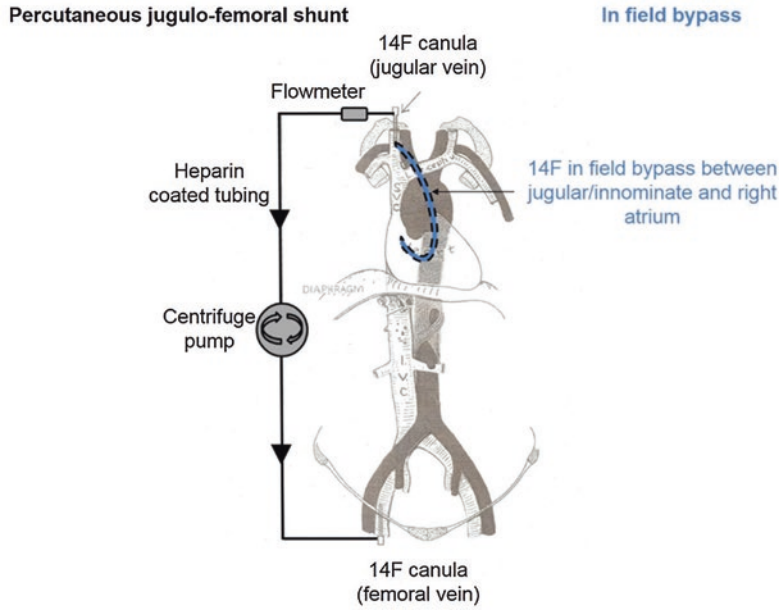

Fig. 2 Two bypass techniques: percutaneous outer-field bypass technique involving mini extra-corporeal life support cannulas (Cemflex Edwards 14F) combined to a centrifugal pump (Left). This approach allows drainage of the upper body in an efficient way and improves venous return, thus avoiding upper body venous hypertension and hemodynamic instability. On the right side of the image: in-field bypass using a sterile 14F tubing between the jugular vein and right atrium (purse-string stabilization of the tubing using a tourniquet)

The outcomes of SVC surgery need to be considered in the context of the more general survival rate of the underlying pathology, especially when it is of malignant origin. Consequently, these survival rates are mainly defined by those of (advanced) lung cancers and can be fairly low (<10 months) in some cases [1, 4], although it should also be mentioned that the average survival of untreated SVC syndrome patients is only 6 weeks. General trends of longer survival tend to be observed (albeit not always to statistical significance level) in patients with N0/N1 disease (versus N2 disease) [4], lesser extent of pulmonary resection [4, 20] and with SVC invasion from a primary tumor rather than a metastasis [4, 21]. Finally, patient selection for surgery seems to be an important aspect to consider in order to maximize the potential benefit from the procedure.

Conclusion/Summary

The "Superior vena cava syndrome" (SVC syndrome) arises following an obstruction of the blood flow in the SVC due to an external compression or to an intravascular thrombosis. It can be of two types: the chronic form develops slowly over time during which alternate drainage pathways develop; the acute form appears suddenly and no alternate drainage pathways can be observed. Management depends on the symptoms and efficiency of these alternate drainage pathways.

Typical symptoms of the SVC syndrome include increased venous pressure of the upper body, which causes facial, conjunctival swelling and head cyanosis, especially when patients lie down. The swelling of the head is more marked in case of acute SVC syndrome, making it potentially life-threatening. In the case of chronic form, symptoms may be mild or almost silent, and hemodynamic instability is rare.

Frequent causes of SVC syndrome are SCLC, NSCLC, lymphoma and mediastinal diseases. The management of SVC syndrome can be medical or surgical (resection and reconstruction). In the latter case, total SVC clamping should be brief to avoid upper body venous hypertension. This can be avoided with the use of bypass devices (jugulo-femoral or in-field bypasses).

Outcomes of selected cases of NSCLC and thymoma invoving the vena cava treated surgically in the context of multimodal therapy are good.

Question 1
Superior vena cava syndrome can be cause by:

A: Chronic infections
B: SVC thrombosis following jugular venous line placement
C: Thymoma
D: Small cell lung cancer adenopathies
E: All of the above

Answer
Correct answer is E

A: Chronic infections such as Tuberculosis or Histioplasmosis can lead to fibrotic lymphadenopathies that can compress the SVC and cause SVC syndrome
B: Venous catheter placement can in some rare cases cause SVC thrombosis that can result in SVC syndrome
C: Thymoma can cause SVC occlusion
D: Small cell lung cancer typically presents as a peripheral lesion with important adenopathies that can cause SVC syndrome

Question 2
Regarding SVC clamping and reconstruction:

A: The right or left subclavian veins cannot be left closed when performing the SVC reconstruction
B: A venous shunt is mandatory during SVC replacement
C: The clamping of a chronically occluded SVC generally causes little hemodynamic instability
D: When choosing the venous prosthesis, a small diameter (less than 10 mm) should be prefered
E: All of the above

Answer

Correct answer is C

A: Right or left subclavian veins can be left closed and reconstruction between innominate to atrium or right jugulo-subclavian confluent to atrium is sufficient

B: A venous shunt is not mandatory for SVC reconstruction but allows more time for reconstruction while avoiding hemodynamic instability

C: A chronically occluded SVC generally has multiple collaterals that compensate for the absence of SVC with little hemodynamic instability at clamping

D: When choosing a venous prosthesis, high diameters 14 mm or more are privileged

E: Wrong

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Approaches and Surgical Techniques for Mediastinal Infectious Diseases

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Key Points

- Acute mediastinal infection is a life-threatening condition that should be promptly recognized and surgically treated.
- The surgical approach is decided based on the type of mediastinal infection and the general condition of the patient.
- Mediastinal debridement and treatment of the source of infection is mandatory.

Introduction

Infectious mediastinal disease (mediastinitis) is a life-threatening infection of the connective tissue of the mediastinum. The mediastinum is defined as the soft tissue located between the lungs and the heart. The Center of Disease control and Prevention in US defines mediastinitis as one of these conditions [1]:

– Growth of a microorganism from mediastinal tissue or fluid
– Surgical evidence of mediastinitis
– Chest pain, fever >38° in combination with purulent discharge from mediastinum or organism isolated from mediastinal drainage.

Mediastinal tissue infection can occur through direct contamination, hematogenous or lymphatic contamination or extension of an infection from a distal source (Fig. 1) (neck, retroperitoneum, lung, chest wall). Mediastinal infections are basically divided into four categories: post-sternotomy mediastinitis, descending necrotizing mediastinitis, acute mediastinitis after esophageal perforation and chronic mediastinitis [2].

Post-sternotomy mediastinitis is a post-operative complication resulting from a wound infection after a sternotomy. In patients undergoing cardiac surgery, its incidence ranges between 0.25 and 5% of patients [2]. Although small in proportion, the number of patients affected by mediastinitis is substantial due to the frequency of cardiac operations [2]. Descending necrotizing mediastinitis results from a cervical infection that spreads from the neck to the mediastinum through the deep cervical fascial plane (Fig. 2). Esophageal perforation causes severe mediastinitis through mediastinal contamination by digestive bacteria and food residues. Chronic mediastinitis is a rare entity that is generally related to granulomatous infection and for which the management is generally non-surgical [3].

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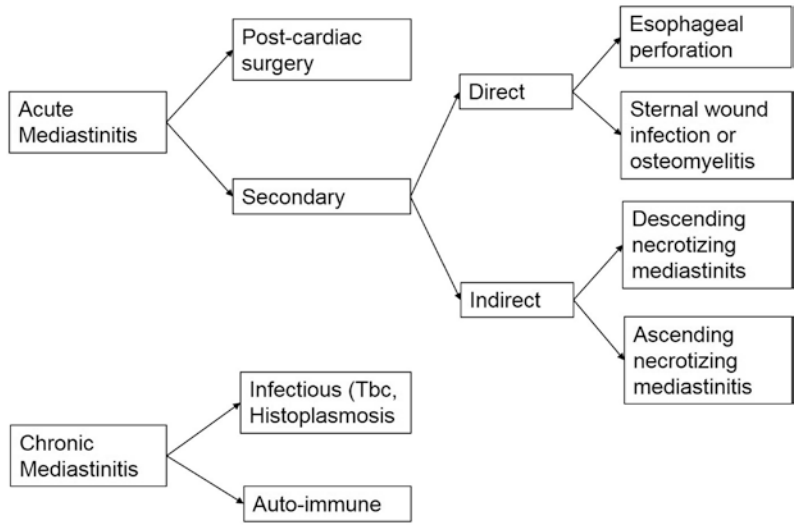

Fig. 1 Classification of Infectious mediastinal disease

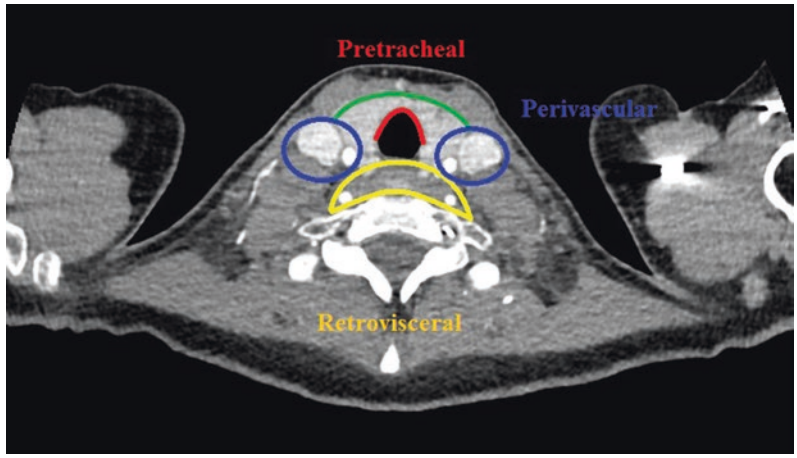

Fig. 2 Cervical fascial planes

Depending on the origin of infection and the clinical features of the patient, mediastinal infections should by managed by experienced multidisciplinary teams including thoracic surgeons, cardiac surgeons, visceral surgeons, oto-rhino-laryngologists and maxillofacial surgeons.

Surgical Considerations

The mediastinum extends from the posterior aspect of the sternum to the anterior surface of the spine and includes the paravertebral sulci. It is limited laterally by the mediastinal pleura and vertically by the diaphragm and the thoracic inlet.

The mediastinum is artificially subdivided into three compartments:

Anterior—The anterior compartment extends from the posterior surface of the sternum to the anterior surface of the pericardium and great vessels.

Middle—The middle mediastinum includes the bronchi, the heart and pericardium, the hila of both lungs, the lymph nodes, the phrenic nerves, the great vessels, and the trachea.

Posterior—The posterior mediastinum includes the azygos vein, the descending aorta, the esophagus, the lymph nodes, the thoracic duct, and the vagus and sympathetic nerves.

The cervical fascial planes are an access source of infection to the mediastinum in descending necrotizing mediastinitis. Thus, an oropharyngeal infection can spread along the fascial planes of the neck communicating to the mediastinum and causing severe infection. Cervical fascia layers separate the local anatomy in three distinct compartments: retro-visceral, pre-tracheal and perivascular (Fig. 2) [2, 4, 5]. The retrovisceral space, which is behind the pharynx and the esophagus, is the most frequent communication channel from the neck to the posterior mediastinum and is involved in more than 70% of descending necrotizing mediastinitis. Rarely, this space can be contaminated by osteomyelitis arising from vertebra. The pre-tracheal space extends anteriorly in the retrosternal plan or the pre-tracheal plan up to the carina. It does not generally extend beyond that point and can provoke pleural and pericardial effusion. The perivascular space can also extend through the carotid sheath with potentially lesion of the cranial nerve or hemorrhage due to vessel erosion.

Clinical Presentation

The clinical presentation of mediastinitis can range from a stable minimally symptomatic patient to a severely ill patient whose life is threatened. Vital signs generally include tachycardia and fever as well as retrosternal or interscapular pain with chest wall irradiation.

Diagnosis

In cases of a history and clinical examination compatible with mediastinitis, subsequent examinations can help as adjuncts to the diagnosis. A chest X-ray can sometimes be sufficient to elaborate the diagnosis of mediastinitis if air can be seen in the mediastinal compartment and pleural effusion is present. Cervico-thoracic CT-scan is generally the best-suited radiological exam to diagnose mediastinitis and define its underlying cause. The presence of air bubbles (pneumomediastinum) may suggest anaerobic infection or esophago-tracheal perforation. Pleural or pericardial effusions are also important signs of extended infection to the pleural or pericardial cavity. In case of suspicion of esophageal perforation, esophagogram with gastrografin can confirm the diagnosis although false negative situations have been reported in 10 to 25% of patients [3]. Baryum should be avoided due to the potential risk of induced mediastinal inflammation. Endoscopic exams (panendoscopy, bronchoscopy or esophagoscopy) should be carried out if esophago-tracheal perforation is suspected on radiological exam. Repetitive CT-scan should be performed when the patient's condition fails to improve after optimal surgical management to visualize contro-lateral or abdominal extension of the infection.

Post-sternotomy Mediastinitis

Post-sternotomy mediastinitis results form a wound contamination during surgery or after surgery. It is rarely related to blood-borne contamination. Most frequently, a post-operative mediastinitis will appear in a subacute manner within 14-30 days post-surgery, although it can appear up to a year after surgery in case of late infection [2, 6]. Post-sternotomy mediastinitis is defined by the presence of micro-organisms in the mediastinal tissue or evidence of infection by histopathological exam. Signs of mediastinitis include purulent production at the site of the surgical wound with local edema, redness, tenderness and sternal instability. Additional signs might include fever, poor surgical recovery and elevated inflammatory markers. Sternal infections are stratified into superficial or deep infections. In case of late infection, the patient may present sternal instability, subcutaneous abscess or sterno-cutaneous fistula. Despite progresses in prevention, post-operative mediastinitis is associated with a poor short- and long-term outcome and a reported mortality rate ranging from

10 to 47% [2]. Factors associated with post-sternotomy mediastinitis have been reported to be: (1) *pre-operative*: obesity and diabetes mellitus and uncontrolled hyperglycemia; *peri-operative*: long operation duration, longer aortic clamping, bilateral use of the internal mammary arteries, and redo operations; *post-operative:* long stay in the Intensive Care Unit and post-operative respiratory insufficiency [2]. Bacterial subtypes involved in post-sternotomy mediastinitis generally originate from the skin i.e. *Staphylococcus aureus* (40 to 60% of cases), *Staphylococcus epidermidis* or coagulase negative staphylococcus (15 to 25% of cases). Gram-negative bacilli (*Escherichia coli*, *Enterobacter*, *Klebsiella, Pseudomonas, Proteus, Acinetobacter*) [7] are encountered in 20 to 25% of cases. The infection can be polymicrobial in 10 to 15% of cases. Culture can be negative in 5 to 10% of cases. Candida mediastinitis is generally related to immunosuppression, is difficult to treat and is associated with a high mortality rate.

Diagnosis

The CT scan is the examination of choice. It can show sternal disruption, free gas bubbles underneath the sternal plate and anterior mediastinal fluid collection.

Surgical Management

Large broad-spectrum antibiotic treatment should be started and adapted to the culture and antibiogram results. Methicillin-resistant *Staphyloccocus aureus* (MRSA) is found in 20% of infected sternotomy sites, and 20% of all organisms in infected sternotomy sites are gram-negative organisms. Multiple regimens are available for use with mediastinitis patients and antibiotic therapy is usually long, ranging from weeks to months if sternal osteomyelitis is present. One study suggests that 4–6 weeks of therapy is adequate for most patients [8].

Cardiac surgeons generally manage post-sternotomy mediastinitis surgically. The optimal approach is decided based on two important elements: sternal stability and sternal bone viability. Post-sternotomy mediastinitis has been classified into four groups [6]. In groups 1 and 2, the sternum is stable and the sternal bone viability reasonable. In group 3, the sternum is unstable and the sternal bone is viable with sufficient viability. In group 4, the sternum is unstable and the sternal bone viability is necrotic and insufficient. Different approaches have been described for the surgical management of post-sternotomy mediastinitis including: open dressings, direct primary closure, closed irrigation negative pressure wound therapy and sternal reconstruction with vascularized tissue (muscle, omentum). The extent of infection will dictate the exact surgical approach.

Asymptomatic sterile sternal dehiscence, also named sternal non-union, is usually not considered a mediastinitis. Occasionally, patients have abrupt separation of the sternum in close proximity to cardiac surgery, necessitating sternal reclosure. However, in case of pain or intolerance due to clicking and discomfort of the non-union, it may require sternal reclosure. For simple sternal dehiscence, care must be taken to exclude active infection with bacterial exams before rewiring the sternum. Rewiring the sternum constitutes an effective surgical strategy for simple sternal dehiscence without infection yielding reasonable long-term results. Osteosynthesis plates can be also proposed as an alternative.

In case of active mediastinal infection, surgical local debridement is necessary. Failure to adequately debride and sterilize the mediastinum during the first reoperation is the most common cause of repeat postoperative mediastinitis. The optimal strategy depends on the extent and duration of the infection, the condition of the mediastinal structures, and the experience of the surgeon. Operative exploration includes reopening the previous sternotomy and debridement of necrotic and infected tissue. Then, depending on the local status, primary or delayed closure is decided. [6]

In case of delayed procedure, the use of negative pressure wound therapy is proposed in addition to local debridement. Vacuum-assisted closure facilitates wound healing by increased perfusion of the wound, facilitated granulation tissue formation, and removal of fluid. The negative pressure in a sternal wound is most often applied at a continuous pressure of −125 mmHg [9]. The wound is packed and changed every after 2 to 4 days until adequate granulation tissue is present. Placement of multiple layers of paraffine at the bottom of the sternum is recommended to avoid right ventricular lesion during changing dressing. Clinical status and biological parameters allow to determine whether the wound is sterile and requires closure. Often, two to four dressings are required to sterilize the wound. Once the wound is healed, the sternum can be safely rewired and the skin closed. Because vacuum-assisted systems are portable, patients can be mobilized earlier and minimize pulmonary complications.

In type 3 and 4, sternal instability mandates further treatment. Viability of sternum should be assessed and sternal stability improved by using plates or clips. Vacuum therapy is generally performed until complete healing and sternal stability is achieved. When the wound shows adequate granulation tissue, a muscle flap can be used to cover sternal debridement and definitive closure can be achieved by using muscle flaps like pectoralis major or rectus abdominis muscles. Both surgeon's experience and patient factors influence the type of flap procedure used. If a large anterior retrosternal dead space exists, it must be obliterated in order to achieve healing [6].

Descending Necrotizing Mediastinitis

Descending necrotizing mediastinitis (DNM), is a life-threatening mediastinal infection originating from the oropharyngeal region and extending into the mediastinum along deep cervical fascial planes. Etiologies commonly include dental abscesses (in particular of the second or third molar) or oropharyngeal infections such as peritonsillar abscesses (Table 1). Polymicrobial bacterial presence

Table 1 Etiology of acute infectious disease of the mediastinum non post-sternotomy

Descending necrotizing mediastinitis	Odontogenic infections Peritonsillar infections Pharyngeal infection Oropharyngeal perforation Cervical trauma Epiglottitis Parotitis Suppurative thyroiditis Sinusitis Sternoclavicular infection Vertebral osteomyelitis Post-operative infection after thyroidectomy, tracheostomy Suppurative thrombophlebitis of the jugular vein Jugular IV drug abuse
Acute mediastinitis	Iatrogenic perforation of the esophagus Trauma Esophageal tumor Boerhaave's syndrome Caustic perforation Perforation of the trachea Pancreatitis

(*Streptococcus pyogenes*, *Streptococcus viridans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Peptostreptococcus* species, *Fusobacterium nucleatum*, *Prevotella* species, *Bacteroides melaninogenicus*, *Actinomyces*) reflects the oro-pharyngeal origin of the infection [3, 10]. Diabetes mellitus, alcoholism, malnutrition and immunosuppressive status are predisposing risk factors and may also delay healing. The disease primarily affects the young men with average age between 35 and 40 years. Estrera et al. defined the diagnosis of DNM when criteria were included [10]:

- Clinical manifestation of severe oropharyngeal manifestation
- Demonstration of characteristic radiological features of mediastinitis
- Documentation of DNM at operation
- Establishment of relationship between oropharyngeal infection and development of DNM.

The cervical infection may propagate in the fascial spaces of the head and neck and spreads into the mediastinum developing phlegmon, necrosis, abscess formation or sepsis. The cervical infection spreading to the mediastinum is facilitated by the mediastinal loose areolar tissue poorly vascularized, the gravity, the breathing and the negative intrathoracic pressure [3–5]. Knowledge of the cervical fascial planes is crucial to understand the different pathways and complications of cervical infections. There are three different spaces through which mediastinal spreading is possible. The pre-tracheal space is involved in approximately 8% of cases and generally originates from pharyngeal infections such as epiglottitis or laryngitis, or following thyroid surgery. The plane ends caudally at the carina and between both pleura laterally. It can sometimes provoke a pericardial or pleural effusion. The vascular space is invaded generally by odontogenic infections that tend to spread to the anterior mediastinum in 12% of cases. The retropharyngeal space spreads to the posterior mediastinum and is responsible of 70% of descending necrotizing mediastinitis cases originating from oropharyngeal infections [11].

This type of mediastinitis presents a high mortality rate (11–40%, depending on the extent of the infection) and can be complicated by severe sepsis or multi-organ failure if rapid treatment is not initiated [2]. Infections circumscribed to the upper carinal region present smaller mortality rates (10%) than infections extending underneath the carina (30%).

The diagnosis of descending mediastinitis is clinical and radiological (Fig. 2). Although the cervical component is easy to recognize, the mediastinal infection is less evident clinically, which can cause surgical delays. Clinical signs point towards the initial oropharyngeal infection ranging from dysphonia, dysphagia, otalgia, trismus, deviation of the uvula. These symptoms are accompanied by systemic symptoms such as fever and hypotension. Contrast-enhanced cervicothoracic CT-scan show large-sized mediastinal adenopathies and/or increased density in adipose tissues. In some cases, concomitant venous thrombosis and myositis may be present. Descending mediastinitis can be difficult to distinguish from a more benign deep neck infection, which might delay the proper diagnosis and onset of treatment.

Surgical Management

In case of acute mediastinitis, antibiotic therapy is rapidly initiated but does not preclude early surgical management. Administration of broad-spectrum antibiotic treatment should cover both aerobes and anaerobes of oropharyngeal origin. Surgical drainage remains the gold standard, but the approach for optimal mediastinal debridement remains controversial.

Various surgical techniques have been described to manage descending mediastinitis and all involve cervical and mediastinal debridement with broad opening of the involved fascia. A team of surgeons including oto-laryngologists, maxillofacial and thoracic surgeons generally collaborate to manage the patient. A double

lumen tube is generally placed to be able to manage both pleural cavities [3].

Endo proposed a simple classification to select the most appropriate surgical management depending on the extent of infection [12]. In upper mediastinal infection situated above the tracheal carina (type I), a simple trans-cervical drainage can be sufficient. If the infection extends to the lower anterior mediastinum (type IIA), trans-cervical approach should be combined with a sub-xiphoidal drainage and/or thoracic drainage if necessary. For invasion of the posterior mediastinum (type IIB), bilateral thoracotomy is generally recommended.

Cervical region debridement is generally performed through a collar incision. This allows optimal access to all deep fascial planes [13]. In case of odontogenic infection, maxillofacial surgery should be undertaken to control the local source of infection. The involved cervical spaces needs to be opened, drained and all necrotic tissues debrided. Cervical wound can be left open and healed by second intention. Most cases are closed with extensive drainage [14]. The mediastinum can be reached anteriorly following the pre-tracheal plane to the carina by blunt dissection, and posteriorly in the retroesophageal plane.

The mediastinal surgical approach depends on the extent and the location of the infection. For upper mediastinitis located above the tracheal carina (type I), cervicotomy and trans-cervical drainage are considered sufficient for localized debridement of thymus and pericardial fatty tissue and drainage. Video-mediastinoscopy-assisted drainage is also described as a treatment option for cervically localized infections. However, cervical debridement in combination with thoracic approach presents better survival when compared to cervical debridement alone. Different invasive surgical approaches have been reported to properly debride mediastinum in extended infection (type II). The procedure should include opening of the mediastinal pleura on a longitudinal axis and removal of all necrotic tissues. Approaches range from percutaneous drainage (thoracostomy tubes, CT-guided drainage of abscess) to more invasive incisions including sub-xiphoidal access, sternotomy [11], thoracotomy [14], clamshell incision [15] or VATS [16]. Each of the mentioned methods presents advantages and disadvantages. Median sternotomy has been proposed for anterior debridement, but seems inadequate to reach posterior mediastinum and the lower part of pleural cavities for decortication. Clamshell incision have also been proposed as alternative to median sternotomy with great facilitation to reach posterior mediastinum and inferior pleural cavities. Both approaches may present potential risk of phrenic nerves lesions, secondary sternal dehiscence or osteomyelitis. However, Kocher et al. reported recently on 16 patients treated by sternotomy (n = 8) or clamshell (n = 8) with good outcomes [11]. If unilateral mediastinal and pleural infection is present, postero-lateral or anterior thoracotomy is considered to be the best approach allowing exposure of prevertebral and paresophageal spaces and ipsilateral access of the mediastinum and pericardium. There is potentially no risk of sternal osteomyelitis. Nowadays, thoracoscopy is gaining greater acceptance with growing experience and allows optimal visualization of the entire pleural cavity and upper and lower mediastinal debridement as well as pleural and pericardial drainage. It has to be noted that aggressive debridement which is best accomplished by open approaches is essential to prevent persistent and progressive disease requiring re-operation. Indeed, minimally invasive approaches have been reported with reoperation rates up to 30% in comparison to 10% in case of open approaches [2]. Additional tracheostomy should be discussed when airways are compromised due to severe oropharyngeal inflammatory edema. This situation should be discussed before extubation because reintubation may be impossible in case of severe cervical and esophageal edema.

Negative pressure wound therapy can also be applied as adjunct to surgery in pleural cavity in cases of severe mediastinal infection. Vacuum therapy has been shown to promote wound healing with accelerated granulation tissue formation, decreased wound bacterial load, removal of

excessive interstitial fluid, improvement of tissue oxygenation, and wound volume reduction. We recently published a study where 27 consecutive patients with severe intrathoracic infections of various etiologies were managed by intrathoracic VAC therapy [17]. We found that VAC therapy was efficient to control intrathoracic infections. In addition, VAC devices allow chest wall closure without affecting chest wall integrity.

Mediastinitis After Oesophageal Perforation

Mediastinal infectious disease following an esophageal perforation is the second-most frequent cause of mediastinitis after post-sternotomy mediastinitis. Approximately half of all perforations of the esophagus are iatrogenic. Traumas (ingestion of foreign bodies; wounds, caustic lesions) or spontaneous perforations (Boerhaave's syndrome) account for most of the other half of esophageal perforations. This type of mediastinitis is characterized by high mortality rates, especially in cases where management is delayed even by a few hours. Leakage of esophageal or gastric fluids into the mediastinum usually rapidly evolves to sepsis and/or multi-organ failure. The clinical outcome depends on etiology, localization and delay until treatment. Spontaneous esophageal perforations carry a death rate of approximately 15% (due to the frequent late diagnosis in such cases), iatrogenous perforations of approximately 13% and perforations following ingestion of a foreign body around 2%. Perforations of the lower part of the esophagus carry a higher death rate than those of the upper part of the esophagus (11% versus 6%) [2, 7].

Risk factors for spontaneous esophageal perforation have been associated with prior esophagus pathologies such as gastro-esophageal reflux, ulcerative disease, malignancies or prior radio-/chemotherapies. It is noteworthy that some (5–10%) esophageal perforations are asymptomatic and that the clinical signs of acute mediastinitis might not always manifest themselves in a clear-cut or specific manner. In the case of iatrogenic acute mediastinitis, symptoms of pain (in the neck or between the shoulders) or of dysphagia immediately or in the hours following an endoscopy must be treated as highly suspect. Chest X-ray will evidence signs of an enlargement of the superior mediastinum, and sometimes also show pleural effusions. Cervico-thoraco-abdominal CT-scan with intravenous and oral contrast-enhancement will enable visualization of the localization of the esophageal perforation and of the exact extension of the infection in the peri-esophageal compartments (Fig. 4). Esophagoscopy should be performed to confirm the exact size of the perforation and rule out any malignancy.

Surgical Management

Broad-spectrum antibiotics covering aerobe and anaerobe bacteria should be promptly started. Oral fluid and food intake should be suspended and proton pump inhibitors should be started to avoid excessive acid reflux. Additional antifungal therapy might be discussed in immunosuppressed patients. Naso-gastric tube should not be inserted without visual control in order to avoid lesion size increase by manipulation.

The localization of the perforation (cervical, thoracic), the underlying disease (tumor), the pleural contamination and the delay of diagnosis will dictate the surgical management.

Esophageal perforation can be managed conservatively when perforation is minimal and that there are no signs of local or systemic infection. Iatrogenic cervical perforations are frequently managed non-operatively as their anatomical confinement from surrounding structures makes infectious spread less likely. However, the patient should be closely monitored. Early parenteral feedings or jejunostomy should be started for nutritional support.

Esophageal primary repair has been reported in historical and more recent series [18]. This is generally performed very early after diagnosis as the chances of success diminish drastically

after 72 h of perforation. Generally, a coverage of the repair by vascularized tissue such as omentum/muscle flap is required to ensure proper healing. This surgery is associated to mediastinal debridement. The choice of flap is related to perforation location. We generally use intercostal muscle, latissimus dorsi or pectoralis muscle flaps for middle or upper esophageal perforation, whereas diaphragm or omentum are used for lower esophageal lesions. A naso-gastric tube is inserted during repair to decompress the stomach, avoid contamination of biliary liquid and promote local healing. In case of cervical perforation, a left cervicotomy along the sternocleidomastoid muscle is generally indicated for debridement and primary repair associated with local drainage. In case of thoracic esophageal perforation, a right sided thoracotomy on the 5th intercostal space is generally proposed for middle perforation whereas lower esophageal perforation is preferentially managed by left thoracotomy in the 6th or 7th intercostal space.

Recently, esophageal perforation managed by endoscopy (covered stents) has shown interesting results in selected patients with small tears, absence of systemic signs of infection or patients who cannot undergo surgery (important comorbidities) (Fig. 3). However, stent placement can only prevent further extraluminal soiling with no effect on the contaminated mediastinum which should then be debrided by thoracotomy or VATS [2].

When extensive esophageal necrosis is present, primary repair is not possible and different techniques can be proposed: esophageal

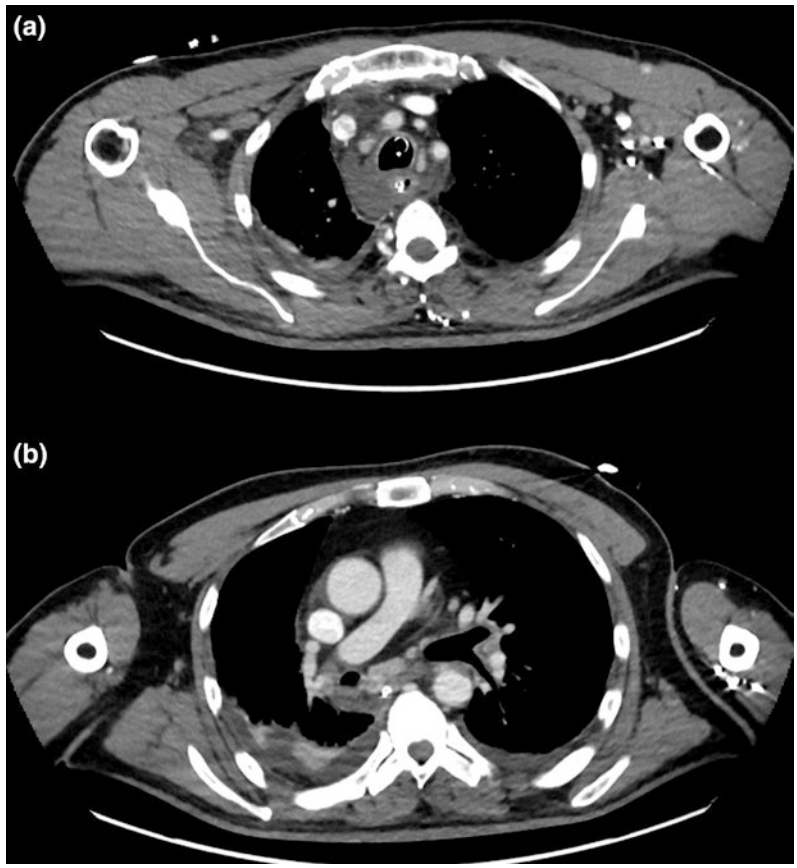

Fig. 3 **a, b** Chest CT-scan showing descending necrotizing mediastinitis with edema of the middle mediastinum, right pleural effusion. The patient underwent successful cervical debridement by cervical incision and right thoracotomy for mediastinal debridement and pleural decortication

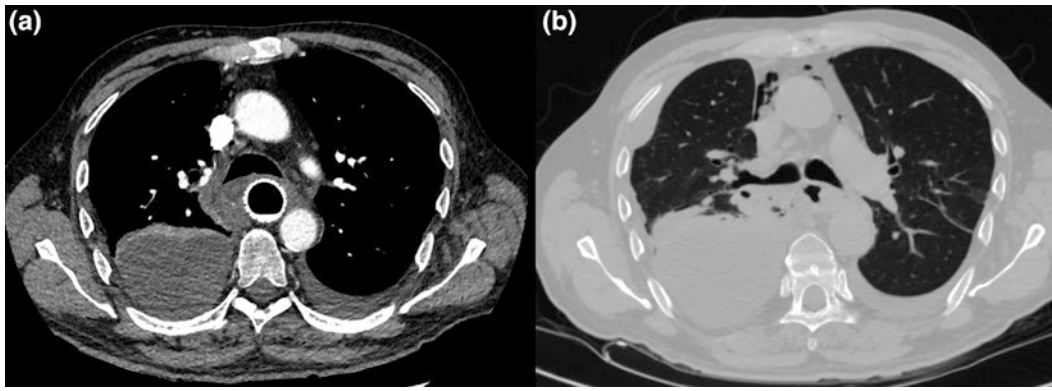

Fig. 4 **a**, **b** Esophageal perforation with pneumomediastinum and right pleural effusion. The patient was first managed with stent placement and right thoracoscopic mediastinal debridement and pleural decortication

exclusion, low esophageal exclusion, or even esophagectomy. Diversion should be reserved in hemodynamically unstable patients and/or if repair is not possible due to the size of the defect and the friability of the surrounding tissue, typically in presence of necrotic gastric tube consecutive to esophagectomy. Diversion requires resection of the affected esophagus, cervical esophagectomy and local debridement and drainage. In case of hemodynamic instability, esophagectomy can be delayed until the patient is stabilized. In selected patients, perforation repair can be managed by closure of the esophageal defect by the use of muscle patch. Extrathoracic muscle flaps can be used to patch the defect to avoid primary closure suture. The muscle is sutured along the border of the esophageal defect with interrupted stitches [19].

Chronic Mediastinitis

Chronic mediastinitis, also known as sclerosing mediastinitis, is characterized by a slow, fibrotic development. This fibrotic process may be the consequence of different etiologies: infectious, immunologic, genetic or toxic [20]. It can induce a narrowing of the airways, of the esophagus, of the pericardium and of mediastinal vascular structures.

The infectious causes of chronic mediastinitis are most frequently due to Mycobacterium tuberculosis. The most frequent fungal infection thought to induce chronic mediastinitis are those due to Histoplasmos (Histoplasma capsulatum). The mediastinal fibrotic reaction is not directly due to the infection but, via an indirect mechanism as yet poorly understood, to an over-active immunologic response of the mediastinal lymph nodes. Worldwide, Histoplasma capsulatum is encountered in the Americas, in Africa, Asia and Australia, most frequently in regions where the ground is covered by large quantities of bird or bat droppings. Histoplasma capsulatum is rarely reported in Europe. Only a small minority of patients infected by Histoplasma capsulatum develop chronic mediastinitis. This might suggest that the appearance of chronic mediastinitis is multifactorial and that it might encompass some degree of genetic predisposition to the over-active immunologic responses involved in this disease. When the suspected cause is an infection by Mycobacterium tuberculosis, one observes an invasion of granulomatous adenopathies into the mediastinum, which may induce a large fibrotic process resulting in compression of other organs (airways, great vessels or esophagus). Non-infectious mediastinal fibrosis can be present in the context of immunologic disease like, Behcet syndrome, sarcoidosis, mediastinal Hodgkin lymphoma or after mediastinal radiotherapy. Chronic mediastinitis can also be associated with auto-immune diseases like retroperitoneal fibrosis, Riedel thyroiditis, sclerosing cholangitis, erythematous lupus or rheumatoid polyarthritis [7].

Most patients remain asymptomatic and mediastinal lesions are generally incidentally found on radiological exams. Symptoms are related to local compression of mediastinal structure like dysphagia (esophagus), dyspnea (trachea, pericardium, heart) facial blush (superior vena cava).

Chest CT-scan can evidence mediastinal infiltrations and calcified lymph nodes. Fibrotic tissue may surround mediastinal vessels resulting in vascular occlusions and collateral vascularization, sometimes of large magnitude. Chest MRI might reveal mediastinal masses with decreased T2 signal and assess the extent of the disease, in particular the vascular invasion forms. It is less useful to visualize calcified zones.

Chronic fibrosing mediastinitis should be closely monitored in case of signs of superior vena cava compression or insufficiency of other mediastinal organs. The mean interval between appearance of symptoms and death issue is generally 6 years.

Management

There is no curative treatment for chronic mediastinitis. Some antifungal therapies have been reported for chronic mediastinitis of fungal etiology, but their exact effect is controversial. Some studies report that amphotericin B has been used with some degree of success. Modest benefits have been reported following treatments by systemic corticoids in case of immune fibrosis or fibrosis secondary to sarcoidosis. Mycophenolate Mofetil have been reported beneficial by slowing the fibrotic process due to the effect on fibroblasts. Successful treatment by Rituximab have also been reported in the literature [20].

In the absence of compression of major mediastinal structures, surgery is rarely recommended to manage chronic fibrosing mediastinitis. It is unclear whether there are ways to minimize the development of superior vena cava syndrome or cardiac compression by surgical debulking early in the process. In rare cases, palliative surgery may be helpful to free airways or esophagus from undue compression. These carry non-negligible bleeding risks, given the generally fibrotic or calcified environment. Endoscopic management might be useful to place endobronchial or endovascular stents and stabilize localized fibroses.

Conclusion/Summary

In conclusion, acute mediastinitis is a rare but potentially lethal infectious disease. Prompt diagnosis is mandatory to avoid delay and related morbidity. Management should be discussed within a multidisciplinary team to decide the optimal surgical approach. Extensive mediastinal debridement and associated treatment of the underlying cause is the cornerstone of the surgical management.

Self-study

Question 1

Which statement is false for the diagnosis of mediastinal infectious disease:

1. A Chest X-ray may show pneumomediastinum
2. Cervico-thoracic CT-scan is the main radiological exam
3. Baryum esophagogram is indicated in case of oesophageal perforation
4. Pneumomediastinum may suggest anaerobic infection or esophago-tracheal perforation.

Answer

1. A chest X-ray can sometimes be sufficient to elaborate the diagnosis of mediastinitis if air can be seen in the mediastinal compartment
2. Cervico-thoracic CT-scan is generally the best-suited radiological exam to diagnose mediastinitis and define its underlying cause
3. In case of suspicion of esophageal perforation, esophagogram with gastrografin can confirm the diagnosis. Baryum should be avoided due to the potential risk of induced mediastinal inflammation. **FALSE**

4. Yes, air bubbles in the mediastinum is suggestive of esophago-tracheal perforation or anaerobic infection.

Question 2

In management of descending necrotizing mediastinitis, which statement is false:

1. Antibiotic therapy should be rapidly initiated once diagnosis is established
2. The retropharyngeal space is responsible of 70% of descending necrotizing mediastinitis cases originating from oropharyngeal infections.
3. Surgical management involves cervical and mediastinal debridement
4. For upper mediastinitis located above the tracheal carina, sternotomy allows optimal mediastinal debridement.

Answer

1. Antibiotic therapy is rapidly initiated and should not preclude early surgical management. Administration of broad-spectrum antibiotic treatment should cover both aerobes and anaerobes of oropharyngeal origin.
2. This type of mediastinitis presents a high mortality rate (11–40%, depending on the extent of the infection) and can be complicated by severe sepsis or multi-organ failure if rapid treatment is not initiated.
3. Various surgical techniques have been described to manage descending mediastinitis and all involve cervical and mediastinal debridement with broad opening of the involved fascia.
4. In upper mediastinal infection situated above the tracheal carina (type I), a simple transcervical drainage can be sufficient FALSE.

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Minimally Invasive Thymectomy

Huang Margaret and Giuseppe Aresu

Key Points

Minimally invasive approaches for thymectomies have become more and more popular.

Several studies have demonstrated the clinical benefit as well as the oncological non inferiority when compared to the traditional open approaches.

Here we described the most common minimally invasive approaches to the mediastinum.

Introduction

Thymectomy is a common surgical procedure undertaken in the field of thoracic surgery and is most frequently indicated in certain patients with myasthenia gravis (MG) or thymic tumours. However, there is ongoing debate regarding the optimum surgical technique, as with the advent of endoscopic technology, a wide range of minimal access techniques have gained popularity over the last few decades. These techniques have been developed with the aim of achieving equivalently radical and safe resections while imparting other benefits to patients, including enhancing recovery and improving cosmesis.

The anterior mediastinum is a narrow and fragile space that contains multiple vital structures. It can therefore be difficult to instrument via a minimal access incision. The surgical approach to this space has traditionally been via maximally invasive approaches such as median sternotomy and thoracotomy. However, surgeons have developed a range of minimal access techniques using a variety of incisions, made possible by video- and robot-assisted technologies.

There are no randomized clinical trials comparing various techniques, in part due to the rarity of thymic neoplasms and uncertainty, until recently, regarding the effectiveness of thymectomy in patients with MG. Clinical practice is therefore based mainly on retrospective case series and some surgeons remain concerned as to whether minimally invasive techniques can achieve safe resections comparable to open approaches.

For example, in thymic malignancies, there is concern regarding increased manipulation of the tumour and risk of capsular disruption, tumour seeding, incomplete resection and increased risk for local. Similar concerns exist in surgery for MG, where complete resection including ectopic thymic foci must be performed to achieve optimal results.

This chapter will examine the indications for and principles of thymectomy, as well as discuss

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the advantages and disadvantages of surgical resectional techniques in common use.

Thymectomy for Myasthenia Gravis

Myasthenia gravis is a chronic autoimmune disease in which autoantibodies attack the nicotinic acetylcholine receptor (AChR) at the neuromuscular junction, resulting in skeletal muscle weakness and fatigability. The incidence is approximately 15 per 100,000 people, making it a comparatively rare disease. It most commonly affects women under 40 and both men and women from 50 to 70 years of age.

The thymus gland has long been known to be associated with myasthenia gravis. It is a primary lymphoid organ where haematopoietic progenitor cells called thymocytes undergo maturation to become T lymphocytes, a critical component of the adaptive immune system. The thymus provides an inductive environment, shaping the selection of a population of T cells that are able to respond to foreign pathogens whilst being immunologically tolerant towards self-antigens. It is thought that failure of this process leads to the development of autoantibodies implicated in MG. Of patients with generalized myasthenia, 85% have thymic hyperplasia and 10–15% have thymoma.

Disabling effects include diplopia, dysphagia, ptosis and weakness in muscles of respiration and disease severity is expressed in terms of the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification (Table 1). Diagnosis involves clinical findings, which may include fluctuating weakness, particularly of extraocular and bulbar muscles. Patients may be tested for antibodies and challenged with edrophonium (Tensilon) though the test itself is not innocuous, and may precipitate profound bradycardia or bronchospasm. The ice-pack test improves ptosis in up to 80% of patients with MG, and electrophysiologic testing is especially useful for patients whose results are negative for AChR antibodies.

Treatment regimens are individualized depending on severity, distribution of disease

Table 1 Myasthenia Gravis Foundation of America (MGFA) clinical classification

Class		Symptoms
0		Asymptomatic
I		Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal
II	a b	Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both
III	a b	Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both
IV	a b	Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both
V		Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb

and progression of symptoms. A multidisciplinary team approach to the care of MG patients is essential, requiring input from specialist neurology, anaesthesiology and thoracic surgical clinicians, as required.

Pharmacologic treatment is initiated by neurologists and involves symptomatic and immunomodulating agents, whereas short-term therapy with plasmapheresis and intravenous immunoglobulins are used in patients with life-threatening respiratory or bulbar dysfunction.

Axial imaging with enhancement is required to determine whether patients have a normal thymus, thymic hyperplasia or thymoma. This will determine what surgical intervention may be offered. Patients with thymoma require resection in line with oncologic guidelines (discussed below). In non-thymomatous MG, thymectomy is performed as an option to avoid or minimize the duration of immunotherapy, or if patients fail to respond to an initial trial of immunotherapy, or have intolerable side effects from that therapy.

Thymectomy became a mainstay of the treatment of non-thymomatous myasthenia on the basis of widely varying anecdotal case series. Multiple subsequent observational studies did not confirm the effectiveness of surgical intervention in this population, and it was not until the recent MGTX international multicentre randomized trial comparing thymectomy with prednisolone versus prednisolone alone that Wolfe and colleagues demonstrated improved clinical outcomes with surgery.

In this trial, extended transsternal thymectomy was chosen to allow for reproducibly radical en bloc resection with minimal risk for phrenic nerve injury. Over a period of three years, patients who underwent surgery had a lower time-weighted Quantitative Myasthenia Gravis score, lower requirement for prednisolone and azathioprine, fewer hospitalisations for exacerbation and comparable rates of treatment associated complications.

Patients with ocular symptoms alone or those with symptoms that are well controlled on pharmacological therapy remain a controversial group for surgical resection. Furthermore, the role of thymectomy in pre-pubertal patients with MG remains unclear, but it may be considered in children with generalized AChR antibody-positive MG with unsatisfactory response to or in order to avoid complications of pharmacological therapy.

Surgery should be planned for when patients are stable and have enough physiological reserve to withstand post-operative pain and transiently limited respiratory function. Patients with generalized weakness despite pharmacological treatment undergo plasmapheresis to improve their overall fitness for general anaesthetic and surgery. This has been shown to facilitate freeing the patient from mechanical ventilatory support and improve respiratory function and muscle strength, translating into decreased hospital stay and cost. It is then extremely rare that severe myasthenic symptoms persist that surgery remains contraindicated. Anaesthetic plans vary between centers, with some preferring to use deep general anaesthetic without the use of muscle relaxants. Other may choose cautious use of non-depolarising muscle relaxants and close monitoring to ensure complete reversal of the effects at the end of the operation.

The widely accepted definition of complete thymectomy extends from the left and right phrenic nerves laterally, sternum anteriorly, pericardium posteriorly, subxiphoid space and diaphgram inferiorly and neck superiorly (Fig. 1) [1]. However, as Jaretsky and Masaoka first reported, the distribution of thymic tissue is widely varied, and scattered ectopic foci can be found throughout the mediastinum (Table 2) [1]. It has not been demonstrated whether extra-anatomic thymic tissue contributes to the pathogenesis of MG, as comparisons of clinical outcomes following radical extended versus standard thymectomy have failed to demonstrate superiority. These studies are however limited by their retrospective nature, small sample sizes and limited follow up data. This is significant, as the clinical improvement of thymectomy may not manifest for many months to years.

Preserving the mechanical integrity of the chest wall using minimal access approaches is probably advantageous in these patients, who have respiratory muscle weakness and are

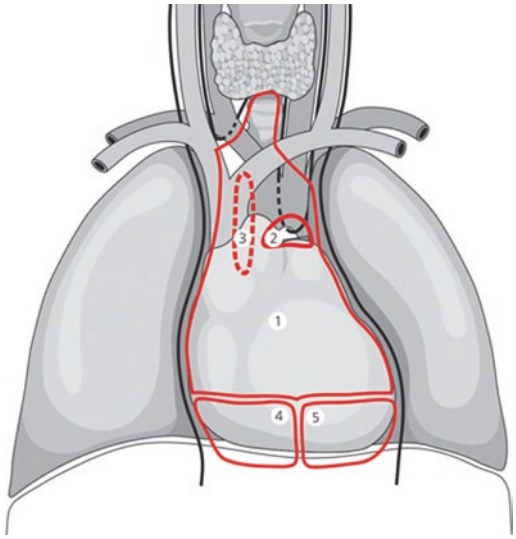

Fig. 1 Areas of the mediastinum dissected during complete thymectomy (1) thymus and perithymic fat, (2) aorto-pulmonary window, (3) aorto-caval groove, (4) right pericardiophrenic angle and (5) left pericardiophrenic angle

Table 2 Incidence of ectopic thymic tissue in thymectomy specimens in an autopsy study

Location	N	%
Perithymic fat	18	36
Aorto-caval groove	1	2
Aorto-pulmonary window	5	10
Right pericardiophrenic angle	0	0
Left pericardiophrenic angle	0	0
Retrothyroid	3	6
Peritracheal	5	10
Right phrenic nerve	2	4
Left phrenic nerve	14	28
Right recurrent laryngeal nerve	2	4
Left recurrent laryngeal nerve	2	4
Retrotracheal	1	2
Periaortic	0	0

therefore at higher risk of subsequent respiratory failure. While the MGTX trial confirmed the utility of thymectomy for MG, there are no randomized trials comparing resectional techniques, therefore controversy persists.

Thymectomy for Thymic Tumours

Primary tumours of the thymus are rare and indolent, and the aetiology of these lesions is not known. The most common histologic type is the thymoma, which arises from the epithelial cells normally responsible for directing T cell maturation. Thymomas frequently also contain infiltrates of abnormally conditioned T cells, which when released into the circulation may be responsible for autoimmune conditions such as myasthenia gravis (discussed above).

These tumours may develop at any age, but are most common between the ages of 35 and 70 years. Distribution between genders is fairly equal, with a slight female preponderance among older age groups. Approximately 30–45% of patients with thymomas will have symptoms of MG, but only 10–15% of patients with MG have thymomas.

Presentation is variable, with a third manifesting with systemic syndromes (including myasthenia gravis, pure red cell aplasia or hypogammaglobulinaemia), a third with local compressive symptoms (including chest pain, cough and shortness of breath) and a third incidentally captured on radiography.

Although rare, thymomas are the most frequently occurring tumours of the anterior mediastinum, accounting for approximately 35–50% of anterior mediastinum masses. Differential diagnoses include lymphoma, thyroid and parathyroid tumours, benign teratoma, malignancy germ cell tumours and benign thymic lesions. It is essential to differentiate thymic malignancies from these other masses prior to treatment. A detailed history and examination are required, as factors including age, gender and the presence of local or systemic signs and symptoms may help to differentiate the type of lesion.

Axial imaging with CT is the preferred modality (Fig. 2). MRI can be useful in distinguishing solid and cystic lesions. CT-PET is not recommended for the routine evaluation of thymoma but is useful in staging lymphoma and evaluating the response to therapy. Elevated levels of alpha-fetoprotein and beta-human

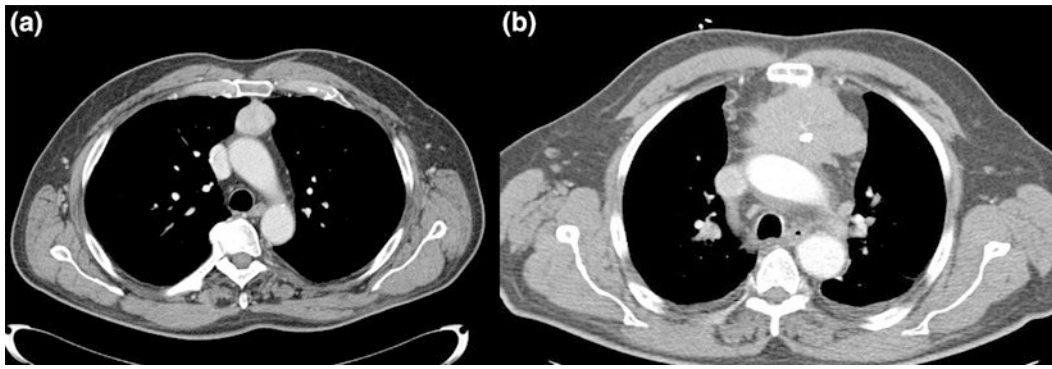

Fig. 2 Appearance of thymic tumour on computed tomography **a** encapsulated and **b** invasive

chorionic gonadotrophin are diagnostic of non-seminomatous germ cell tumours, while elevated lactate dehydrogenase is a common finding in lymphoma [2].

Tumours may be considered benign or malignant depending on capsular invasion. Staging is by the modified Masaoka-Koga system, which is largely based upon the extent of local invasion of the primary tumour, as nodal involvement is infrequent. Tumour extension is directly related to predicted survival. Approximately 50% of thymomas are found to have invaded mediastinal tissue by the time of diagnosis. The International Thymic Malignancy Interest Group (ITMIG) has adopted the Masaoka-Koga staging system with additional definitions (Table 3) [3].

Complete (R0) resection is the standard of care for thymic malignancies, and has been shown to be effective in achieving high cure rates. This requires en bloc resection of the entire thymus gland and surrounding mediastinal areolar tissue. Adjunctive treatment with radiotherapy and chemotherapy are used for stage III and IV thymomas, and improves R0 resection rates. However, the most oncologically effective and safe technique for resection remains subject to controversy. There are no prospective randomized trials on this subject.

The lymph node map for TNM staging of thymic tumours was published by IASLC/ITMIG in 2014 (Table 4). It is recommended that anterior mediastinal lymph nodes are resected for localized thymomas. Additionally, deep intrathoracic lymph nodes should be sampled for invasive thymomas, and should be resected for thymic carcinoma.

During resection of thymic malignancies, care must be taken to keep the plane of dissection beyond the capsule, to avoid direct traction to the capsule and to limit capsular tears and local and pleural contamination by neoplastic cells. Therefore, good exposure and flexibility for manipulation of tissues must be afforded by whichever surgical technique is chosen.

It is recommended that specimens should be routinely marked, as it can be difficult to determine the correct orientation once removed from the patient. Suspicious areas of the specimen should be marked with a stich, and the corresponding area in the operative field should be clipped in case radiation is indicated post-operatively. Other standard areas to be marked include the surface of the specimen adjacent to the pericardium, innominate vein, superior vena cava and right and left pleural surfaces.

Mini-sternotomy

The mini-sternotomy is a variation on the traditional sternotomy approach and can be easily extended to complete sternal splitting if complications arise or restricted access would compromise resection.

Table 3 Masaoka-Koga staging system with International Thymic Malignancy interest group definition of details

Stage	Definition
I	Grossly and microscopically completely encapsulated tumor *This includes tumors with invasion into but not through the capsule, or* *Tumors in which the capsule is missing but without invasion into surrounding tissues*
IIa	Microscopic transcapsular invasion *Microscopic transcapsular invasion (not grossly appreciated)*
IIb	Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium *Gross visual tumor extension into normal thymus or perithymic fat surrounding the thymoma (microscopically confirmed), or* *Adherence to pleura or pericardium making removal of these structures necessary during resection, with microscopic confirmation of perithymic invasion (but without microscopic extension into or through the mediastinal pleura or into the fibrous layer of the pericardium)*
III	Macroscopic invasion into neighboring organ (i.e. pericardium, great vessel or lung) *This includes extension of the primary tumor to any of the following tissues:* *Microscopic involvement of mediastinal pleura (either partial or penetrating the elastin layer); or* *Microscopic involvement of the pericardium (either partial in the fibrous layer or penetrating through to the serosal layer); or* *Microscopically confirmed direct penetration into the outer elastin layer of the visceral pleura or into the lung parenchyma; or* *Invasion into the phrenic or vagus nerves (microscopically confirmed, adherence alone is not sufficient); or* *Invasion into or penetration through major vascular structures (microscopically confirmed);* *Adherence (i.e. fibrous attachment) of lung or adjacent organs only if there is mediastinal pleural or pericardial invasion (microscopically confirmed)*
IVa	Pleural or pericardial metastases *Microscopically confirmed nodules, separate from the primary tumor, involving the visceral or parietal pleural surfaces, or the pericardial or epicardial surfaces*
IVb	Lymphogenous or hematogenous metastasis *Any nodal involvement (e.g. anterior mediastinal, intrathoracic, low/anterior cervical nodes, any other extrathoracic nodes)* *Distant metastases (i.e. extrathoracic and outside the cervical perithymic region) or pulmonary parenchymal nodules (not a pleural implant)*

The patient is positioned as for a standard sternotomy. The sternum is divided up to the third intercostal space and is then transected transversely using an oscillating saw, preserving the internal mammary arteries. A retractor, for example a paediatric Finocchietto, is used to spread the sternum. A hand-held retractor can be used lift the soft tissue above the sternum to improve the view (Fig. 3). For a radical dissection, the mediastinal fat is removed from the diaphragm to the thyroid gland, and from phrenic to phrenic nerve laterally.

The right inferior horn is dissected off the pericardium with its associated pericardial fat. This is clamped, ligated and divided. The right superior horn is freed circumferentially until the thyrothymic ligament is identified. This is divided from the thyroid gland and the ligament is ligated. The freed horns are retracted to the contralateral side, exposing the arterial supply entering laterally from the internal mammary arteries. The rest of the right lobe and its associated fatty tissue is dissected from the area above the phrenic nerve up to the junction of the innominate vein and superior vena cava. The lateral arterial blood supply is ligated and divided.

The left side is carried out in a similar fashion but can be more difficult due to the proximity of the left phrenic nerve to the thymus gland. Once all four horns have been mobilized successfully, the venous drainage into the innominate vein are ligated and divided. Haemostasis is then performed and a chest tube is placed in the retrostenal space. This can be

Table 4 International association for the study of lung cancer/International thymic malignancy interest group lymph node map for thymic epithelial neoplasms (a) anterior region (N1, anterior mediastinal and anterior cervical lymph nodes) and (b) deep region (N2, middle mediastinal and deep cervical lymph nodes)

Region or Lymph Node Group	Boundaries
Anterior region (N1)	Superior: hyoid bone Lateral (neck): medial border of carotid sheaths Lateral (chest): mediastinal pleura Anterior: sternum Posteromedial: great vessels and pericardium Posterolateral: phrenic nerve Inferior: xiphoid process and diaphragm
Low anterior cervical: pretracheal, paratracheal, perithy-roid, precricoid/delphian (AAO-HNS/ASHNS level 6, IASLC level 1)	Superior: inferior border of cricoid cartilage Lateral: common carotid arteries Inferior: superior border of manubrium
Perithymic	Proximity to thymus
Prevascular (IASLC level 3a)	Superior: apex of chest Anterior: posterior sternum Posterior: anterior SVC Inferior: carina
Para-aortic, ascending aorta, superior phrenic (IASLC level 6)	Superior: line tangential to superior border of aortic arch Inferior: inferior border of aortic arch
Supradiaphragmatic/inferior phrenic/pericardial (along inferior poles of thymus)	Superior: inferior border of aortic arch Anterior: posterior sternum Posterior: phrenic nerve (laterally) or pericardium (medially) Inferior: diaphragm
Deep region (N2)	Superior: level of lower border of cricoid cartilage Anteromedial (neck): lateral border of sternohyoid muscle and medial border of carotid sheath Posterolateral (neck): anterior border of trapezius muscle Anterior (chest): aortic arch, aortopulmonary window-anterior border of SVC Posterior (chest): esophagus Lateral (chest): pulmonary hila Inferior: diaphragm
Lower jugular (AAO-HNS/ASHNS level 4)	Superior: level of lower border of cricoid cartilage Anteromedial: lateral border of sternohyoid muscle Posterolateral: lateral border of sternocleidomastoid muscle Inferior: clavicle
Supraclavicular/venous angle: confluence of internal jugular and subclavian veins (AAO-HNS/ASHNS level 5b)	Superior: level of lower border of cricoid cartilage Anteromedial: posterior border of sternocleidomastoid muscle Posterolateral: anterior border of trapezius muscle Inferior: clavicle
Internal mammary	Proximity to internal mammary arteries
Upper paratracheal (IASLC level 2)	Superior: superior border of manubrium, apices of lungs Inferior: intersection of lower border of innominate vein with trachea; superior border of aortic arch
Lower paratracheal (IASLC level 4)	Superior: intersection of lower border of innominate vein with trachea; superior border of aortic arch Inferior: lower border of azygos vein, superior border of left main pulmonary artery

continued

Table 4 (continued)

Region or Lymph Node Group	Boundaries
Subaortic/aortopulmonary window (IASLC level 5)	Superior: inferior border of aortic arch Medial: ductus ligament Inferior: superior border of left main pulmonary artery
Subcarinal (IASLC level 7)	Superior: carina Inferior: upper border of lower lobe bronchus on left; lower border of bronchus intermedius on right
Hilar (IASLC level 10)	Superior: lower rim of azygos vein on right, upper rim of pulmonary artery on left Inferior: interlobar region bilaterally

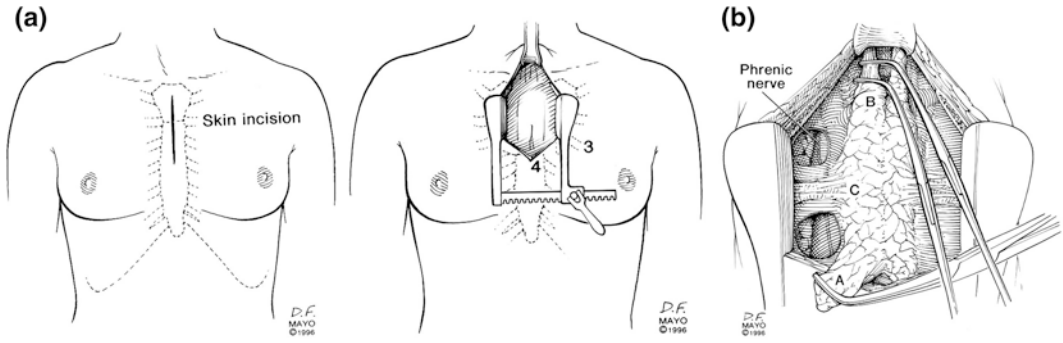

Fig. 3 **a** Skin incision for upper partial sternotomy, **b** sternal retractor in place and anatomical relations of thymus gland

through a subxiphoid incision if the pleurae are not opened, or lateral to the internal mammary artery in an intercostal space. The sternal edges are wired and skin is closed [4].

Lateral Intercostal Access

Video-assisted thoracoscopic surgery (VATS) via lateral intercostal trochar or utility thoracotomy incisions can be performed with a unilateral or bilateral approach. Axial imaging prior to surgery is useful to determine whether this approach is suitable, for instance to determine the size of a tumour or whether it is well encapsulated.

For the right unilateral approach, general anaesthesia is established and a double lumen endotracheal tube or single lumen endotracheal tube with carbon dioxide insufflation is placed. Ports are placed along the right anterior axillary line, conforming to the mammary crease. The patient may be positioned in the lateral decubitus position, tilted away or supine. The right arm is held abducted for exposure of the axilla. The right lung is isolated and the inferior aspect of the thymus is mobilized. The dissection plane is extended cranially, taking care to preserve the integrity of the right phrenic nerve. The left aspect of the thymus is mobilized from the pericardium overlying the ascending aorta and thymic veins are clipped and divided. The right and left thymic horns are dissected free. A utility thoracotomy allows the extraction of the specimen at the end of the procedure, and can be extended into a classic posterolateral incision if the intervention cannot be continued thoracoscopically. Thymic malignancies are inserted into a plastic bag before extraction to prevent tumour spillage and seeding. A chest drain is placed via the trochar or utility thoracotomy.

This approach is advantageous in providing more operative space, visualizing the right phrenic nerve and superior vena cava. The left phrenic nerve, pericardial fat and aorto-pulmonary window are, however, less well visualized. Conversely, the left VATS approach provides less operative space, thereby potential difficulty with port placement particularly in cases with cardiomegaly, but easier dissection of the left pericardial fat and left phrenic nerve aorto-pulmonary window. The bilateral VATS approach allows fuller visualization of the mediastinum and both phrenic nerves, facilitating radical resection.

The bilateral VATS approach can be achieved with the patient in supine position. Ports are inserted in a similar arrangement, and the mediastinal pleural is incised just anterior to the phrenic nerve. The base of the left thymic lobe is then mobilized and retracted superiorly. The thymic and perithymic fatty tissue are moibilised en bloc with the specimen, allowing exposure of the underlying pericardium and aorta. The thymus is carefully dissected along the innominate vein and the thymic tributaries are clipped and divided. The dissection is continued to the innominate-superior vena cava junction. The cervical horns are mobilized and swept inferior with the specimen. One maximal mobilization is achieved on the left, the ports and instruments are withdrawn. The right sided ports are then placed, and dissection is completed along the innominate-superior vena cava junction. The venous thymic branches are clipped and any residual attachments divided, allowing the specimen to be removed.

Retrospective analyses have demonstrated several advantages of intercostal VATS thymectomy over traditional sternotomy. These include reduced intra-operative blood loss, earlier removal of chest drains, reduced requirement for blood produces, reduced inflammatory cytokine response, reduced length of stay, superior cosmesis and comparable oncological and symptomatic outcomes in thymic tumour resection and MG respectively. However, these studies are limited by small sample sizes, potential selection bias and need for longer follow-up data [5–7].

Transcervical Access

The patient is placed in supine position and general anaesthesia is instituted. If an arterial line is used, it should be placed in the left arm, as intermittent compression of the innominate artery during the operation may result in falsely low blood pressure measurements. A supportive roll is placed under the shoulders to allow hyperextension of the neck. This approach may therefore not be appropriate for patients with cervical spine abnormalities. The anterior chest and cervical region are prepared, in case median sternotomy is required.

A curved collar incision is made between the sternocleidomastoid muscles. The caudal skin flap is dissected in the subplatysmal plane down to the sternal notch and the ligament is divided vertically to improve exposure of the substernal plane. The cranial skin flap is dissected to the inferior border of the thyroid gland and the strap muscles are separated along the midline raphe (Fig. 4). The upper poles of the thymus gland are found lying immediately superficial to the inferior thyroid vein and posterior to the strap muscles. This may be prohibitively difficult if the patient has had previous thyroid surgery.

The left superior pole is identified and dissected down towards the point at which it merges with the right superior pole. The right superior pole is similarly dissected free and ligatures are placed around both poles to allow gentle retraction. The upper poles meet just above the sternal notch and pass into the chest anterior to the innominate vein.

With the upper lobes freed to the level of the innominate vein, the pre-thymic plane is created with blunt finger dissection to allow the introduction of a Cooper thymectomy retractor (Pilling Company, Ft. Washington, PA), which provides upwards retraction of the sternum. This allows the head and shoulders to fall back and allow direct visualization of the mediastinum. This is more difficult if there has been a previous sternotomy. The upper corners of the incision are retracted to provide counter-traction.

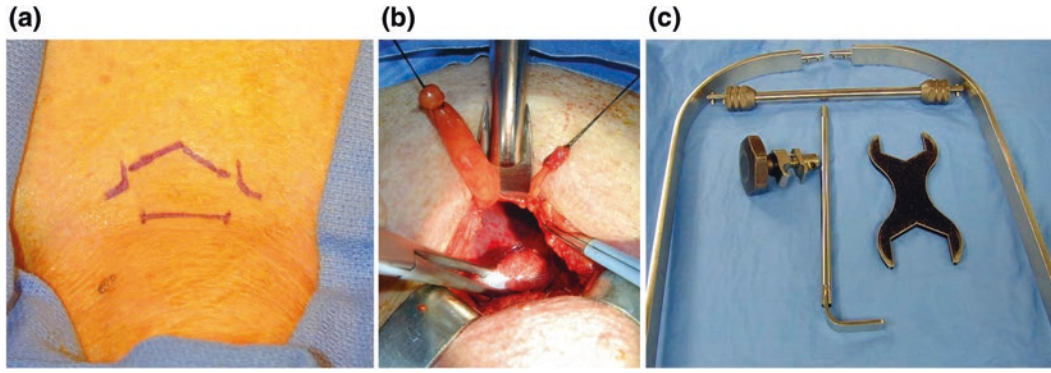

Fig. 4 **a** Landmarks for incision, **b** retractor in situ, **c** Cooper thymectomy retractor

The surgeon wears a headlight and is seated at the head. The thymus is retracted forward and upward to display the veins draining into the innominate vein, which are ligated and divided. Dissection is then carried along the posterior aspect of the thymus into the mediastinum, separating it from the pericardium. If required due to adhesions, a portion of the pericardium may be removed en bloc with the specimen. The tidal volume may be decreased, or lung ventilation suspended for a period of time to assist visualization and instrumentation of the deeper part of the mediastinum. The great vessels can be depressed using an endoscopic sponge to allow dissection close to the aorto-pulmonary window. Small branching blood vessels from the superior vena cava or internal mammaries can be dealt with electrocautery, taking care not to injure the phrenic nerves. Patients who are anaesthetized without a paralytic agent will exhibit diaphragmatic excitation if electrocautery is used in close proximity to the phrenic nerves.

The thymus is generally removed as a complete gland. Inspection of the mediastinum is then performed to ensure any suspicious tissue is removed. Some parts of the mediastinum are less well visualized using this approach, including behind the innominate vein and aorto-pulmonary window. A red rubber catheter is then placed into the mediastinum and brought out slowly as the wound in closed. If either pleura have been opened, the entry point maybe widened to allow evacuation of air with the red rubber catheter during a prolonged positive pressure breath. The patient is extubated and transferred to recovery [8].

Subxiphoid Access

The subxiphoid approach aims to avoid drawbacks such as intercostal nerve paralysis or neuralgia and difficulty visualizing the contralateral phrenic nerve and neck, which can be experienced when using lateral intercostal incisions. The incision allows excellent views of the anterior mediastinum as well as both phrenic nerves and pleural spaces, allowing the surgeon to perform a radical and safe resection. However, the approach is considered not appropriate for patients with high BMI, thoracic cage deformity, cardiomegaly or poor cardiac function, or invasive thymic tumours (stage II–IV).

In a retrospective assessment comparing lateral intercostal and subxiphoid single port thymectomy, blood loss, postoperative oral analgesia use and hospital stay were reduced in the subxiphoid group [9].

Experienced VATS surgeons can acquire the skills to perform this technique with a relatively short learning curve. Challenges for surgeons learning the technique are the longer subcutaneous tunnel, smaller operative angle and more instrument interference.

Under general anaesthesia, patients are placed in a supine position with a roll beneath the scapulae to allow for maximal chest extension. Selective one lung ventilation is used during the procedure.

A 4-cm-long horizontal subxiphoid incision is made if the infrasternal angle is within normal limits or more than 70°. Alternatively, if the infrasternal angle is less than 70°, a longitudinal incision is made (Fig. 5). The xiphoid process is resected to provide a widened operative view. The sternum can be elevated using a Cooper retractor. Blunt finger dissection creates a retrosternal tunnel between the incision and the thoracic cavity and a wound protector is placed to further optimize the view. Any obstructing anterior mediastinal adipose tissue is removed. A 10 mm 30° angle thoracoscope (Karl Storz, Tuttlingen, Germany) is used to visualize the mediastinum. The phrenic nerves, internal mammary vessels and cranial aspect of the mediastinum can be visualized throughout the procedure, minimizing the risk of injury.

Selective ventilation of the left lung is commenced and the right pleural cavity is opened. Electrocautery dissection of pericardial and epiphrenic fat pads is performed and then the right lobe of the thymus is identified and dissected from the pericardium and ascending aorta. Care is taken to fully visualise the innominate vein and superior vena cava junction prior to dissection of the thymic horn from the underlying innominate vein. The thymic veins (of which there are usually 2–4) are identified prior to the confluence with the innominate vein and ligated using a LigaSure device.

Single lung ventilation is then switched to the right lung, allowing the left pleural cavity to be opened. The left pericardial and aorto-pulmonary window adipose tissue are dissected prior to completing dissection of the left thymic horn. The thoracoscopic instruments may compress the heart in this brief period, particularly if there is cardiomegaly. Patients with impaired heart function may therefore experience haemodynamic compromise. The freed thymus and mediastinal fat are then removed en bloc via the subxiphoid incision.

A 28 Ch chest drain is placed in each pleural cavity and the subxiphoid incision closed around the drains. Patients are extubated and are able to receive intensive physiotherapy from day zero with minimal discomfort [10].

Variations on this approach have been developed to include transcervical-subxiphoid thymectomy [11], subxiphoid with lateral intercostal thymectomy, subxiphoid dual port thymectomy and transxiphoid robotic thymectomy, which reported similar early surgical outcomes to subxiphoid single port thymectomy [12].

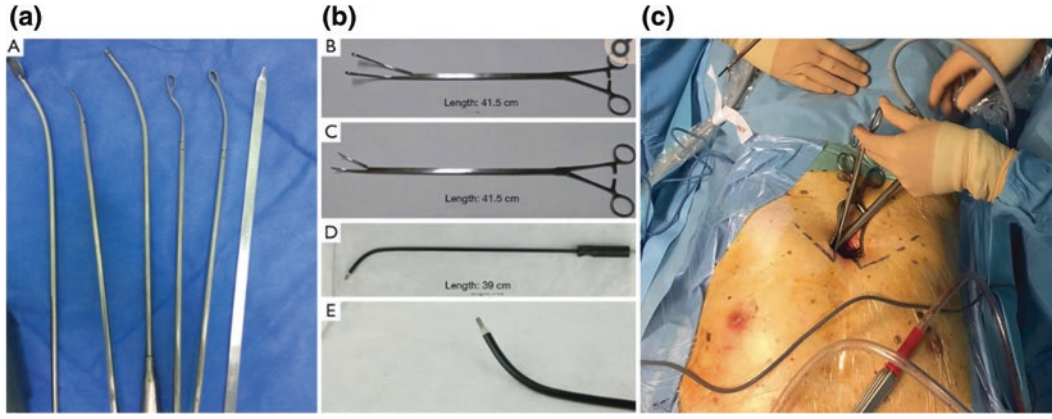

Fig. 5 **a** Instruments designed for subxiphoid surgery, **b** landmarks for subxiphoid incision (costal margin) and **c** position of instruments intra-operatively

Summary

Minimal access approaches have gained international popularity for performing advanced surgical procedures at experienced centers, and technologies have evolved rapidly to support innovation. The benefits of thoracoscopic approaches compared to open techniques have been well documented in reports studying functional and oncologic outcomes in a wide range of thoracic surgical procedures. These include but are not limited to reduced blood loss and post-operative pain, increased early mobilization and hospital discharge and reduced institutional costs.

Experience of a growing range of techniques has increased across the world despite the paucity of robust comparative data. Many studies have been published comparing different minimally invasive approaches to open resection in patients with thymic tumours and myasthenia gravis. The majority are retrospective case series with inherent limitations and biases. To date, there are no randomized controlled trials comparing techniques, therefore no consensus exists as to which approach is superior. Randomised controlled trials are urgently required to inform the community about best practice, though adequately powered multi-centre non-randomised prospective studies may be the best possible realistic alternative.

Ultimately, the best approach should be determined by the patient's characteristics, the surgeon's experience and comfort level, and the ability to adhere to the tenets of MG or oncologic surgery. The planned or completed thymectomy, whether for MG or thymic tumour, should not be compromised to achieve a minimally invasive operation. It is important to maintain the mindset that transition to an open approach should be considered a standard expectation rather than complication. However, if an equivalent resection can be achieved by minimally invasive means, then an advantage is conferred to the patient in terms of enhanced recovery.

Self-study

1 What are the most frequent indication for thymectomy?
   (a) Coronary artery disease
   (b) Lung cancer
   (c) lymphoma
   (d) Bronchogenic cyst
   (e) Thymoma and myasthenia gravis

2 Which one of the following is not frequently described Myasthenia Gravis symptom?
   (a) Diplopia
   (b) Dysphagia,
   (c) Ptosis
   (d) Weakness in muscles of respiration
   (e) Chest pain

Correct Answers

1: e
2: e

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Mediastinal Pseudotumours

Claudiu E. Nistor and Alexandru Mihai Cornea

Key Points

- Mediastinal pseudotumors comprise tumor-like lesions or non-tumor lesions with the origin outside of mediastinal borders which invade mediastinum
- Mediastinal pseudotumors comprise non-tumor lesions developed from visceral mediastinum
- Mediastinal pseudotumors have clinical expression (mediastinal syndrome) and radiological findings (mediastinal mass) same to mediastinal tumors

Definitions

Mediastinal pseudotumors comprise (1) tumor-like lesions or non-tumor lesions with the origin outside of mediastinal borders which invade mediastinum; and (2) non-tumor lesions developed from visceral mediastinum [1]. These mediastinal pseudotumors have clinical expression (mediastinal syndrome) and radiological findings (mediastinal mass) same to mediastinal tumors [1].

Mediastinal pseudotumors which behave clinically and radiologically as mediastinal tumors might be classified either by their ***origin*** (cervical, supradiaphragmatic, diaphragmatic, subdiaphragmatic masses (Table 1); or after the ***mediastinal compartment*** involved (anterior, visceral mediastinum, or paravertebral groove) (Table 2); or masses which come from the thoracic skeleton or the thoracic spinal cord.

Non-tumoral mediastinal lesions may develop as mediastinal tumors and may be classified according to the mediastinal compartments where they develop as anterior, visceral, or paravertebral masses of mediastinum (Table 3) [2].

Intrathoracic Goiters

1. Cervico-Mediastinal Goiter

Anatomy

It develops from the cervical region and descends into the visceral mediastinum covered anteriorly by the peritracheal fascia and posterior and medially by great vessels (Fig. 1) [3, 4]. Most of the goiter plunged into thorax are

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Table 1 Mediastinal pseudotumors (depending on their origin)

Cervical	• Cervico-mediastinal goiter • Cervical cystic Hygroma
Supradiaphragmatic	• Lung tumors • Diffuse pleural mesothelioma • Solitary fibrous pleural tumors • Closed pleural effusion • Hydatid pulmonary cyst
Diaphragmatic	• Cyst tumors • Diaphragmatic tumors • Diaphragmatic relaxation
Subdiaphragmatic	• Hiatal hernias • Hernia Morgagni Larrey • Bochdaleck hernias • Subphrenic abscess • Pseudocyst of the pancreas • Renal ectopia
Thoracic skeleton/spinal cord canal	• Ribs bone tumors • Costal-vertebral tumors • Costovertebral cold abscesses • Meningocele

anterior and lateral to trachea (paratracheal) [1]. A part of them such as posterior goiter develops retrotracheal or even retroesophageal [5, 6]. The development of cervico-mediastinal goiter is possible only in the following situations: (1) patients with prior thyroid surgery, when the lower portion of plunged goiter with retrovascular location protrudes in the anterior mediastinum, anterior to the aortic arch, and (2) when a thyroid cancer develops on a plunged goiter and invades the prevascular space and the structures of the anterior mediastinum [1].

Symptoms

Patients with cervico-mediastinal goiter might be asymptomatic, the mass being discovered on routine chest X-ray, or like a cervical tumor mass, with dysphagia, stridor, cough, or wheezing [7]. Occasionally the disease can manifest itself through severe dyspnea that reveals acute respiratory failure by acute tracheal compression.

Clinical Examination

Frequently manifests as a cervical pseudotumor, mobile with deglutition [8]. Neck venous dilatations (the collar of Stokes) explain the brachiocephalic venous trunk compression mechanism, between thyroid pseudotumor and rigid structures of the upper thoracic aperture [1]. Occasionally hypothyroidism or hyperthyroidism signs may be present.

Chest X-ray

It shows the existence of a broadside mass in the upper part of the mediastinum, with the deflection of the cervical trachea to the right or left in 80–95% of cases [1]. Posterior goiters can bend the anterior trachea and the posterior esophagus (on the lateral chest radiography).

CT Examination

Reveals an intrathoracic mass, well defined edges, non-homogeneous structure, with hypodense areas and calcifications and increased uptake for intravenous iodate contrast [9, 10].

MRI Examination

It is not usually necessary in the diagnosis of cervico-mediastinal goiter. It allows to highlight the report of goiter with the large vessels and cervical origin of the goiter.

Table 2 Mediastinal pseudotumors (depending on the involved mediastinal compartment)

Anterior Mediastinum	Visceral Mediastinum	Paravertebral ditches
• Sternocostal tumor • Hernia Morgagni Larrey	• Hiatal hernias • Pseudocyst of the pancreas • Cervico-mediastinal goiter • Cervical cystic Hygroma	• Bochdaleck hernias • Costal-vertebral tumor • Costovertebral cold abscesses • Meningocele

Table 3 Non-tumoral mediastinal lesions [2]

I. **Anterior mediastinum**
• **Hypertrophic thymus** (Hyperplasia) • **Ectopic mediastinal goiter** (Embryogenesis, descends with the thymus and heart) • **Vascular aneurysms** (fusiforms/sacculars) with origin in the visceral mediastinum, with developing into anterior mediastinum. They are (1) **arterial aneurysms** (ascending aorta, brachiocephalic trunk or innominate artery, pulmonary artery); and (2) **venous aneurysms** (superior vena cava, brachiocephalic veins or innominate veins). • **Cardiac aneurysms** • **Pericardial cysts** • **Anterior Mediastinitis/Mediastinal abscess** (1) ACUTE—esophageal perforation, descending necrotizing mediastinitis, postoperative (cardiac surgery); (2) SUBACUTE; (3) CHRONIC (granulomatous, fibrous)
II. **Visceral mediastinum**
• **Cervico-mediastinal goiter** (with dystrophic developing and gets down pretracheal where peritracheal fascia does not allow the descent prior to large large vessels) • **Vascular aneurysms** (aortic arch/ductus arteriosus) • **Pulmonary artery ectasis** (pulmonary valvular stenosis or due to left to right intracardiac shunt) • **Abnormalities of pulmonary veins** [venous dilatation (varicose veins), anomalous pulmonary venous return or scimitar syndrome radiology in radiology] • **Lung hilar congestion** • **Ectasia of systemic veins** • **Double Aortic Arch** • **Mediastinitis Mediastinal Abscess**
III. **Paravertebral groove**
• **Vascular aneurysms** (descending aorta) • **Esophageal pathology** (oesophageal diverticulitis, megaesophagus, malformations (esophageal duplication)) • **Extralobar pulmonary sequestration** • **Intrathoracic extramedullary haematopoiesis** (intratoracic paravertebral location) • **Mediastinitis/Mediastinal abscess**

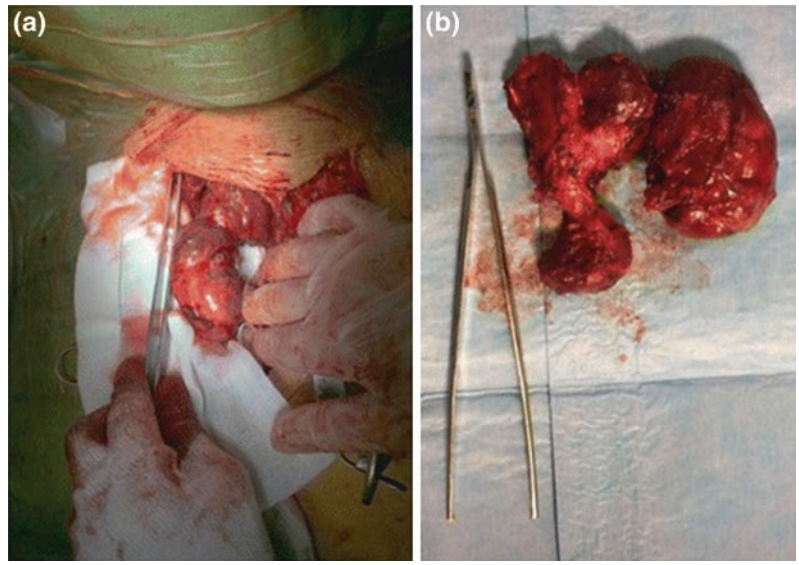

Fig. 1 **a** Intraoperative isolation of mediastinal thyroid through sternal splitting. **b** Cervical and mediastinal thyroid after excision. From [4] [This article is published under license to BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited]

Echography has a low sensitivity in the exploration of a cervico-mediastinal masses [8]. It can, however, differentiate between a parathyroid cyst and a thyroid lesion.

Thyroid scintigraphy with radioactive iodine
Can differentiate the goiter from other mediastinal pseudotumors [9].

2. **Mediastinal ectopic goiter**

Anatomy
It develops as ectopic thyroid tissue found in the anterior mediastinum nearby thymus. Vascularization has specific anatomical characteristics, which arises from the intrathoracic vessels and not from the neck [11]. It is accompanied by the presence of normal cervical thyroid gland, from which is anatomically separated [1].

Clinical examination
This pathological entity can only be discussed in patients who have no history of thyroidectomy (avioding the possibility of incomplete removal of a cervico-mediastinal goiter). Clinical signs are scarce (radiological only) or may have the appearance of a superior mediastinal compression (SMC) syndrome.

Chest X-ray
Reveals anterior mediastinal enlargement because of the thyroid tumor.

CT Thorax Examination
CT is mandatory for tumoral mass location, presented as non-homogeneous, with hypodense areas, calcifications, and increased uptake for intravenous iodate contrast (Figs. 2 and 3) [4, 12].

Thyroid scintigraphy with radioactive iodine
It shows the existence of two separate areas of capture for the radiotracer: one at the cervical level and the other at mediastinal level.

Cystic Lymphangioma (Hygroma)

Anatomy
It is a congenital anomaly of the jugular lymphatic sac, which can be seen from birth or even in utero by fetal ultrasound [13]. It develops from the cervical region, in the proximity of the internal

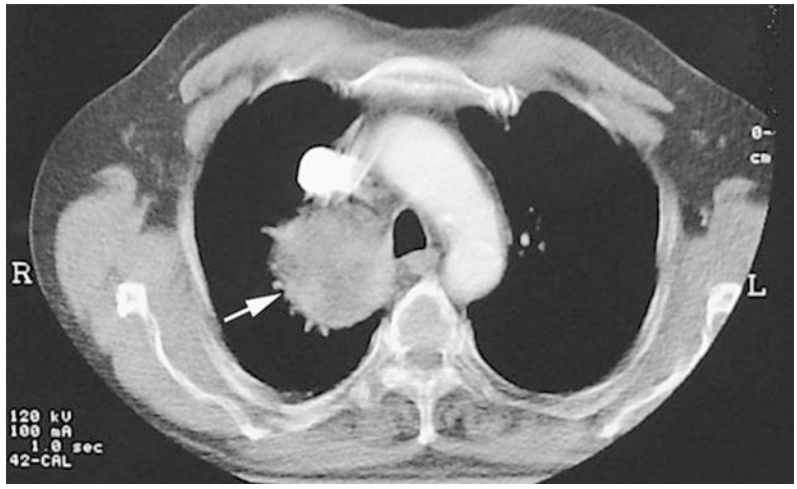

Fig. 2 Contrast-enhanced CT demonstrates an inhomogeneous enhancing mass at the right side of the mediastinum (arrow). From [12]. It is open access. [This article is published under license to BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited]

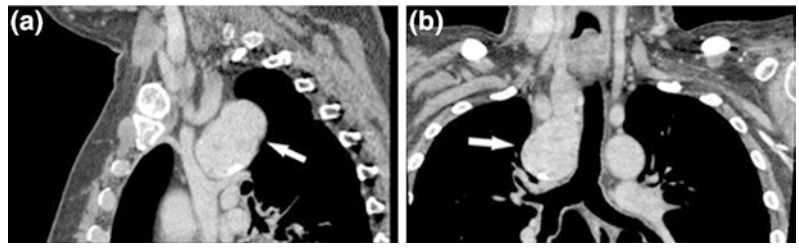

Fig. 3 **a** Lateral view and **b** Frontal view of enhanced-CT scan of neck and chest showing the mediastinal mass (white arrow) and the mediastinal structures around. From [4] [This article is published under license to BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited]

jugular vein and the nerve roots C3, C4 and C5 and descends along the phrenic nerve, protruding into visceral mediastinum between the vein and the subclavian artery, reaching the area of primordial subclavian lymphatic sac. If the development of this anomalies lasts, tracheal or esophageal deviations may occur in the visceral mediastinum or, the cystic formation may pass by the anterior part of the aortic arch, into anterior mediastinum.

Symptoms
Most of the patients have no symptoms. Occasionally breathing issues might be seen at birth, because of tracheal compression or pulmonary infections.

Clinical examination
It is discovered at birth, as a mass in the cervical region. This tumor is soft and can be transilluminated. Occasionally it can be associated with chylothorax [14, 15] or chylopericardium.

Chest X-ray
Chest X-Ray reveals the presence of a mediastinal mass that can impinge the trachea or esophagus of newborn.

Ultrasounds
It can set up the cystic nature of the cervico-mediastinal formation.

CT Examination
It does not offer diagnostic elements in addition to ultrasound, while being irradiant and expensive.

Lesions of Thoracic Cage

These lesions mimic mediastinal tumors and are most commonly seen on the anterior part of the sternum and ribs or chondral joints, or as posterior suppurative vertebral bone processes that spread in the neighborhood structures (paravertebral abscess).

1. **Thoracic spine chordoma**

Anatomy
These tumors develop from the embryonic remnants of the primordial notochord (from which the nucleus of the normal vertebral nucleus pulposus is derived). When these tumors occur at the level of the thoracic vertebral bodies, they can mimic a mediastinal tumor mass because the majority are malignant and have an invasive locoregional character to the sternum and ribs grooves or to the visceral mediastinum structures: trachea or esophagus [16].

Symptoms
Patients might be asymptomatic or may present symptoms related to compression and invasion of vital neighborhood structures: spinal compression (pain, paresthesia, paralysis in the lower limbs), tracheal compression (inspiratory dyspnea) or esophageal (dysphagia).

Clinical examination
Neurological signs as hypomobility, muscular hypotonia, absence of osteotendinous reflexes or tracheal compression are indicators of the

advanced stage of the disease, with locoregional invasion.

Standard radiological examination
These tumors may present as paravertebral masses or it can be highlighted on the radiography as ivory vertebra [17].

Computed Tomography Examination
After Meyer there is vertebral body damage along with soft tissue densities localized anterolateral to the spine [18]. Same authors note the presence of amorphous calcifications in 40% of the studied lesions.

2. **Thoracic vertebral Chondrosarcoma**

It is a rare tumor that develops from the thoracic vertebral body and extends into the costovertebral sulcus or to visceral mediastinum. Symptomatology, clinical examination and paraclinical investigations are like chordoma. It can also evolve as a "dumbbell tumor" invading three vertebral bodies (T5, T6, T7) and with intervertebral protrusion [1].

3. **The thoracic paravertebral abscess**

Anatomy
It is a nontumoral, inflammatory lesion, most commonly tuberculosis related. With its origin is from the thoracic vertebral body, it develops at the level of the paravertebral groove, as a mediastinal mass.

Clinical examination
The clinical picture from asymptomatic or oligosymptomatic forms are ruled out by the phthisis (signs of Bacillary impregnation), forms manifested with the neurological syndrome of bone marrow compression (due to spinal and intervertebral disc destruction).

Chest X-ray
Reveals the existence of a paravertebral mediastinal mass accompanied by radiological signs of vertebral bone destruction (osteolytic lesions, bone deformities, until vertebral collapse).

CT Examination
Notes the fluid character of the mediastinal mass and specifies its localization in the vicinity of areas of vertebral bone destructions.

Lesions of Thoracic Spinal Cord

Anterior Meningocele

Anatomy
It is a greater or lesser protrusion (herniation) of the spinal meninges, through one or more intervertebral holes. This meningeal pouch develops in the form of a cystic mass localized in the paravertebral groove, therefore, from the point of view of the position towards the spine it can be referred to more accurately the lateral meningocele (Fig. 4) [19].

Clinical manifestations
Most meningoceles (85%) are part of von Recklinghausen disease (neurofibromatosis), so they can be missed as neurogenic tumor [20].

Usually there are asymptomatic, being a random radiological discovery. Sometimes posterior chest pain or various neurological manifestations have been reported. Same patients exhibit kyphoscoliosis to the vertebral lesion level [1].

Chest X-ray
It highlights a well-delimited paraspinal mass, accompanied by kyphoscoliosis, erosions in the adjacent dorsal vertebra, widening of the conjugation hole and thinning of the neighboring rib with the lesion.

CT Exam
It is essential to prove the cystic nature of the paravertebral lesion and to set up the relationship with the spine. When there is a diagnostic doubt, CT-myelography with Metrizamide is decisive [21].

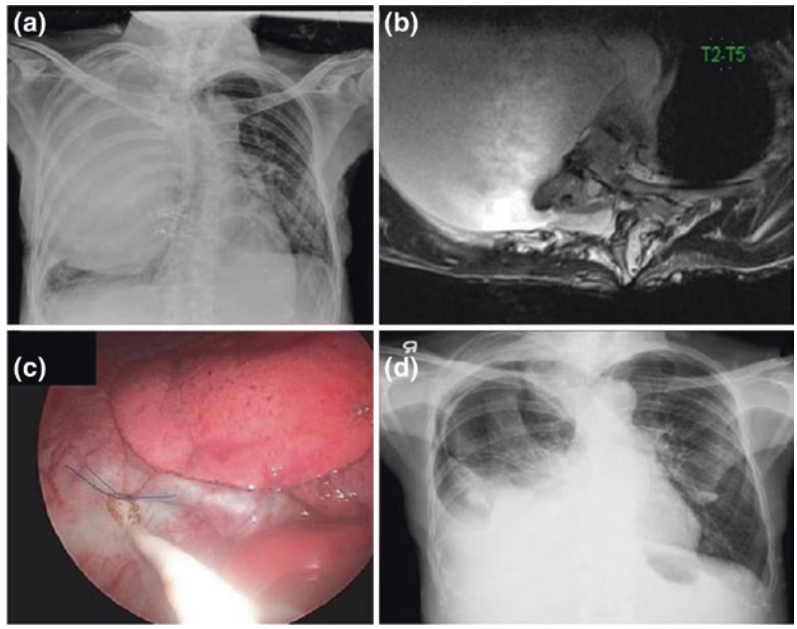

Fig. 4 Chest plain radiograph findings before and after 3 months of thoracoscopic plication. **a** A large opaque shadow was seen in the right lung field with atelectasis of the lower lobe and kyphoscoliosis of thoracic spine was marked. **b** T2-weighted magnetic resonance imaging showed cerebrospinal fluid signal intensity and a meningeal cystic lesion protruding through the right neural foramen at T4. **c** The catheter was inserted into the meningocele, and the purse-string suture was tied under thoracoscopic guidance. **d** Postoperative chest radiograph at 3 months later showed marked regression of the intrathoracic meningocele. From [19].This article is published under license to BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated

Intrathoracic Extramedullary Hematopoiesis

Anatomy

Is an ectopic haemopoietic tissue hyperplasia arising in severe forms of anemia: hemolytic anemia (spherocytosis, thalassemia, sickle cell disease) or in pernicious anemia. The intrathoracically localization is rare and it is most commonly found at the level of paravertebral groove and rarely in anterior mediastinum.

Clinical manifestations

They are dominated by the picture of the anemia and signs of medullar compression (intracanal hyperplastic tissue extension).

Chest X-ray

It reveals the existence of a paraspinal mass, with indistincts limits, found behind the heart [22].

CT Exam and Laminography

It often shows the bilateral nature of the lesion.

Radioactive Iron scintigraphy (Fe 59) or radioactive gold (Au 198)
Confirms the hematopoietic development nature of the mediastinal tissue mass.

Vascular Masses of Mediastinum

The mediastinum is organized as anterior, middle, and posterior compartments limited by, diaphragm, thoracic inlet and pleural cavity.

The anterior compartment borders are sternum anteriorly and pericardium posteriorly, the middle compartment is limited by anterior surface of pericardium and posterior by the anterior surface of the spine and posterior compartment is from ventral surface of spine to the vertebral bodies [23].

The anterior mediastinum comprises thymus and internal mammary vessels, the middle compartment comprises the heart with great vessels, trachea with bifurcation, phrenic and vagus nerves. The posterior compartment comprises the sympathetic chain, intercostal neurovascular bundle, and spinal ganglia.

The vascular masses are mimicking the mediastinal tumors and are accidental radiological findings done for other medical reasons.

CT and MRI are highly diagnostic and can differentiate the vascular masses from mediastinal tumors.

Arterial Aneurysms

Aortic aneurysms

Anatomy, classifications
There are vascular dilatations due to arterial wall weakening which could be genetic or secondary to atherosclerotic disease. There are two main types of aneurysms true or false (pseudoaneurysms).

True arterial aneurysms are characterized by preservation of the arterial wall and false aneurysms are most often post-traumatic and have no a true wall.

Aneurysms can be spindle or saccular (fusiform when whole arterial wall is dilated, and saccular, when the wall yields unilaterally, circumscribed).

Etiology
Aortic aneurysms can be degenerative as in the aortic atherosclerosis or congenital because of connective tissue disorders as in Marfan syndrome, Loeys-Dietz syndrome [24] or Ehlers-Danlos syndrome. The aneurysms might be *anastomotic aneurysm* (after bypass surgery), *dissecting aneurysm* (which usually occurs at the level of aorta by a tear in the internal aortic wall, with the cleavage of the walls due to penetration of the blood into the thickness of the aortic wall), *arteriovenous aneurysm* (erosion by the arterial aneurysm of a neighboring vein and the formation of a fistulas that allows the passage of blood from the artery into a vein). Apart from the cases listed, several other conditions such as infections, vasculitis, traumatisms still play a role in their etiology.

The aneurysms of thoracic aorta are classified in the aneurysms of ascending aorta, aortic arch and descending aorta.

Ascending aortic aneurysms are including the annulus, aortic root and the Valsalva sinuses (Fig. 5 shows a widening of the aorta root from the ring to the sino-tubular area).

The ascending aorta is involved in 40% and the arch and descending aorta are affected in 60% of aneurysms.

Clinical manifestations
Aneurysms are often asymptomatic. A nerve or vein compressive syndrome can cause pain or venous insufficiency. The clinical picture depends on location, size, and aneurysm progression. Thoracic aortic aneurysm is associated with rib erosions and could manifest often as a pulsatile tumor. Mediastinal compressive syndrome is characterized by cyanosis, collateral venous circulation, edema, anginal pain and respiratory disorders.

Aortic dissection consists of a tear inside the aortic layers, with the dissemination of the blood

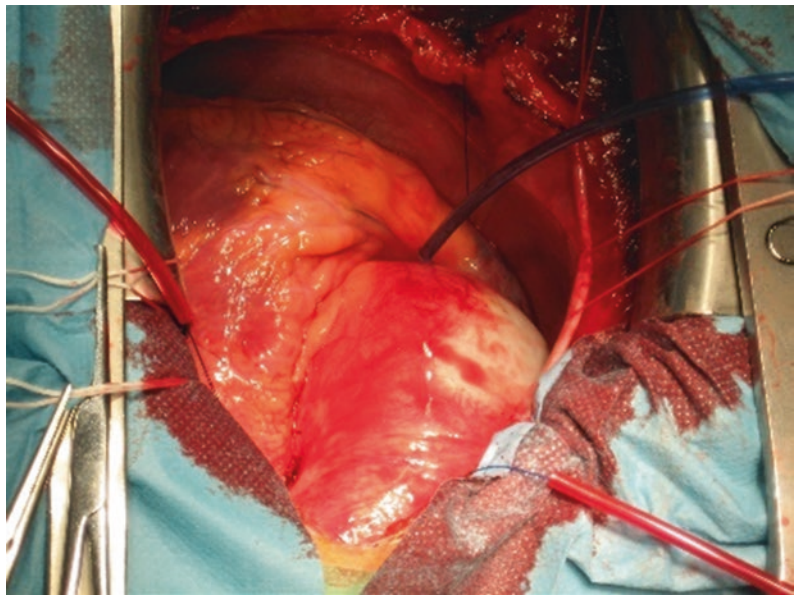

Fig. 5 Aortic root and ascending aortic aneurysm

from the true lumen into a false lumen of the arterial wall within an intimal rupture.

The cause is atherosclerosis, or a medial degeneration of the aortic wall caused by genetic disorders as Marfan or Loeys-Dietz disease and the clinical picture usually is dramatic marked by chest pain, localized in the anterior and posterior thorax, with irradiation in the shoulders, cervical and abdominal-sweating, dyspnea, coma, syncope, leg or visceral ischemia. The prognosis is guarded. Complications are life-threatening and rupture, tamponade, stroke, visceral and peripheral ischemia are the most important.

Standard radiological examination

It is part of the first exploration techniques and supplies insufficient data. The radiological exam highlights the aneurysm in the form of a round shadow, pulsatile mass, which makes the joint body with the aorta (Fig. 6). The radiographic image shows the calcifying of the walls of the dilated vessel. Aneurysm of the thoracic aorta could be accompanied by rib erosions.

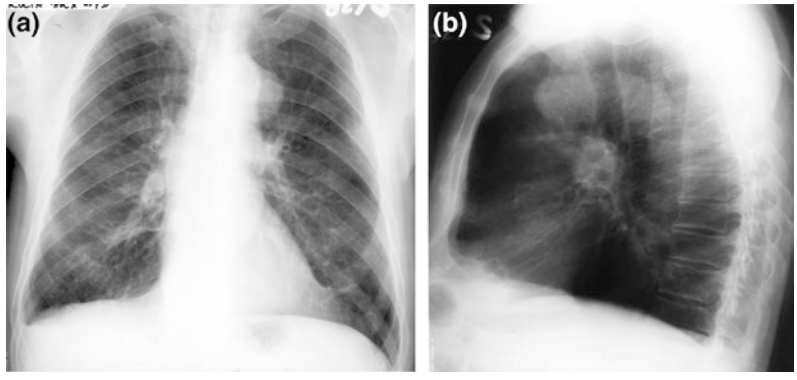

Fig. 6 Aortic aneurysm: Round radiological opacity that makes the joint body with the aorta

The radiological examination reveals an opacity found on the right aortic side when involves the aortic root or Valsalva sinus, or as an increase in aortic arch diameter and a left paravertebral aortic opacity when contains descending aorta.

CT

The aneurysm is an increase of arterial diameter by more than 50% versus normal caliber. Contrast enhanced computed tomography allows correct and reproducible measurement of the aortic diameters. It also supplies data about type of aneurysm (fusiform or saccular), caliber, length, angle, presence of intraluminal thrombus, and morphology of aorto-iliac bifurcation (Fig. 7).

In case of aortic dissection the essential for diagnosis is the evidence of intimal flap, true and false lumen, the presence of thrombus and involvement of branch vessels. Presence of the intimal tear is essential for the diagnosis of dissection and tamponade suggests intrapericardial rupture.

Transthoracic echocardiography

It is particularly useful in diagnostic of the aneurysm of the ascending aorta by measuring its diameter. Transthoracic ecocardiography reveals the aortic valve regurgitation in aortic root aneurysm and can give details of tear in the lumen of the aorta, being diagnostic for dissection.

Transesophageal echocardiography (TEE)

The TEE is particularly useful in analyzing the root, ascending, arch and descending aorta. Intimal tear and the presence or absence of the flow in the false lumen, the extension of the false lumen on the large vessels and descending aorta. The TEE emphasizing the presence of hemopericardium as a sign of rupture of the ascending aorta with or without tamponade effect.

TEE offers data about the diameters of the aorta being a high-value examination.

Angiography

Angiography tends to be replaced by the multislice computed tomography, which has revolutionized cardiovascular imaging, by building 3D models, made by removing the artifacts given by the heartbeat.

The treatment of aortic aneurysms is complex and surgical treatment depends on aneurysmal extension and aortic diameter. For ascending aorta, the landmark is 50 mm diameter for patients with Marfan disease or more than 55 mm for atherosclerotic aorta. If the patient has a moderate or severe aortic regurgitation and a 50 mm ascending aortic diameter has indication for surgery [25]. Aortic root aneurysm surgery tries to preserve the aortic valve [26] and to replace the segment involved of the root and ascending aorta with a conduit and to relocate the coronary ostia in the prosthesis [27]. Another option

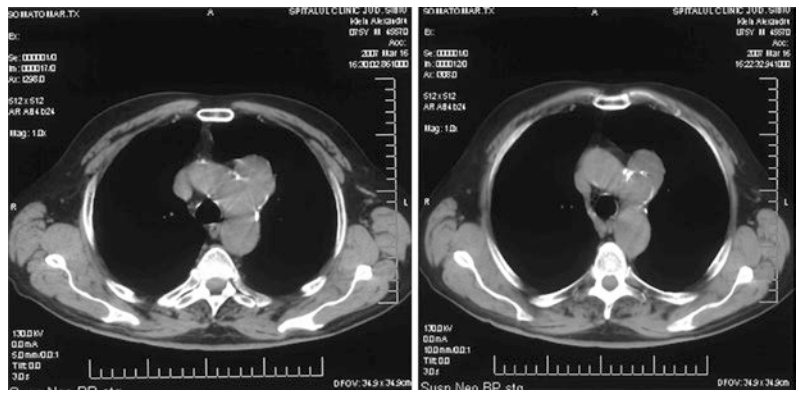

Fig. 7 Computed tomography. Aortic arch aneurysm

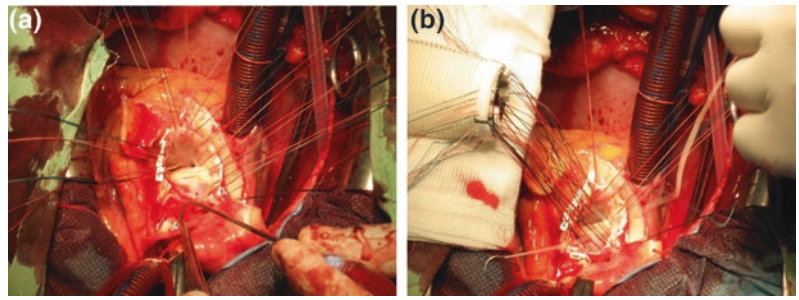

Fig. 8 **a**, **b** Aortic dissection Bentall procedure (aortic root, valve and ascending aortic replacement with composite graft, mechanical prosthesis, and coronary ostia reimplantation in the prosthetic conduit)

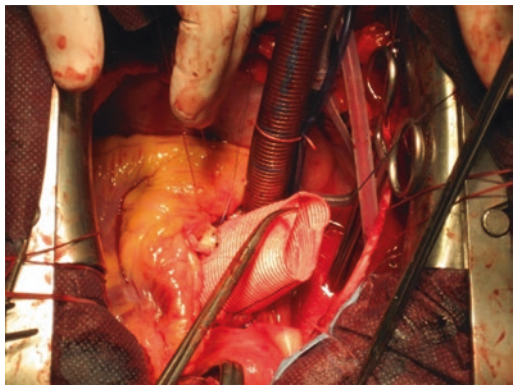

Fig. 9 Reimplantation of the left and right coronary arteries in the prosthetic conduit

is root, aortic valve and ascending aorta replacement with a prosthetic conduct (Bentall operation Figs. 8 and 9). Surgery is performed on cardiopulmonary bypass with moderate hypothermia.

The redo operations for root and ascending aortic aneurysms have additional surgical risks and higher mortality and morbidity [28].

Aortic arch repair is addressed to half (hemiarch replacement) or entire aortic arch with or without use the "elephant trunk technique" on the descending aorta. It also uses the cardiopulmonary bypass with moderate hypothermia and the selective antegrade cerebral perfusion. Another technique uses deep hypothermia without cerebral perfusion or with retrograde cerebral perfusion during the aorta arch replacement. The origin of major branches of the arch are implanted as an island or separately into the conduit.

Descending aortic aneurysms are operated either by open repair or by transaortic endovascular repair (TEVAR). Open repair of descending thoracic or thoracoabdominal aneurysms is indicated if aortic diameter is more than 60 mm for atherosclerotic or more 55 mm for aortic dissection Surgical approach is left thoracotomy prolonged onto the abdomen, with left heart bypass, or by cardiopulmonary bypass with deep hypothermia and circulatory arrest [29], with intercostal and visceral arteries implantation into the prosthesis.

Transaortic endovascular repair (TEVAR) uses endovascular prostheses and are a choice for asymptomatic large (aortic diameter twice than normal) descending aneurysms or symptomatic aneurysms in the absence of connective tissue disorder. A hybrid approach can be performed for an extensive aneurysm of the ascending and descending aorta [30].

Aortic pseudoaneurysms

Are caused by trauma, cardiac surgery related or after aortic infections. Have a remarkably high tendency to rupture. Surgical treatment is not standardized and both open-heart surgery and endovascular procedures for closing the hole in the aorta with stent can be used [31].

Pulmonary artery aneurysms occur in the same circumstances as the aortic aneurysms (genetic mutations, infectious, Behcet-type vasculitis) but are rare.

Can be accompanied by aortic aneurysms or by medial layer fragility and chest X-ray shows an opacity that covers left side of the chest.

Pulmonary artery annulus is dilated, and there is massive pulmonary regurgitation. Sometimes the pulmonary valve can have many cusps [32]. Pulmonary hypertension occurs in more than half of the cases.

Pulmonary valve replacement with a biological prosthesis is a standard procedure with or without a plastic surgery at the level of the pulmonary artery [33, 34].

Pulmonary artery pseudoaneurysms are rare, and can be due to infections, traumas, or iatrogenic maneuvers as the introduction of the Swan Ganz catheter. Surgery is mandatory and consists on aneurysm resection and a pulmonary valve procedure [35]. Pulmonary artery pseudoaneurysm could develop as a chronic erosion due by an aortic arch composite prosthesis [36].

Coronary artery fistulas are aberrant communication between a coronary artery and a cavity of the heart, or one of the large vessels (pulmonary artery, upper vena cava, coronary sinus or pulmonary veins) [37].

Right coronary artery origin is involved in more than half of the cases. Could be congenital or postinfectious, traumatic, etc. They can be asymptomatic or with signs of heart failure. Surgery consists of fistula ligature with or without cardiopulmonary bypass.

Coronary artery aneurysm are coronary arteries dilations and can be congenital or acquired, or secondary to vasculitis or traumatic lesions. When accompanied by coronary artery disease, surgical treatment is routine [38].

Mammary artery aneurysms

Occur in the context of congenital diseases with an aortopulmonary type of circulation. Usually they have no symptoms and are discovered incidentally.

The treatment is surgical and consists of ligature or occlusion by intraarterially coil [39].

Left Ventricular Aneurysm

Left ventricular aneurysm (LVA) is a consequence of acute myocardial infarction or in rare circumstances secondary to sarcoidosis, Chagas disease, congenital disease, or chest trauma (Fig. 10) [10, 16]. A true LVA aneurysm is formed by a dilated ventricular wall and false aneurysm or pseudoaneurysm that is a ruptured ventricle usually covered by pericardium.

The main symptoms angina and dyspnea are common, but other signs as arrhythmias, syncope, or shock could be remarked. Usual complications are rupture, ventricular thrombosis, stroke, peripheral emboli, severe arrythmias or sudden death. Left ventricular aneurysms can be located on anterior wall, inferior, lateral, septal or to the apex.

CT and cardiac MRI are providing anatomical details; and echocardiography is providing information about ventricular kinetics, valvular dysfunction and evidence of intraventricular thrombosis.

Surgical treatment is needed in the presence of angina, heart failure and life-threatening arrhythmias [40]. There are a few surgical techniques depending on aneurysm size and location, or presence of coronary artery disease, and consists on plication of small aneurysms (Cooley procedure), or aneurysmal resection with LV geometric reconstruction Dor procedure (Figs. 11 and 12) [41], Jatene or McCarthy techniques. When coronary artery disease is present the coronary artery bypass grafting must be done on same time with aneurysm resection.

Venous Aneurysms

Intrathoracic veins aneurysms

Superior Vena Cava aneurysms. The dilatation and superior vena cava aneurysms are seldom due to the proximity compression caused

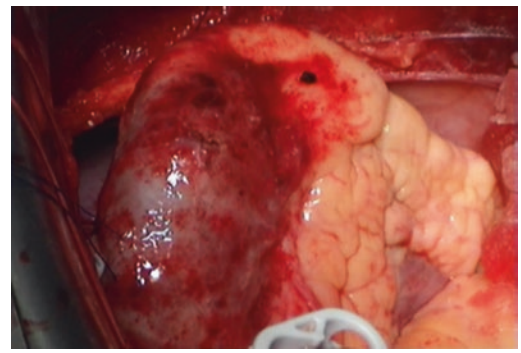

Fig. 10 Apical LV aneurysm

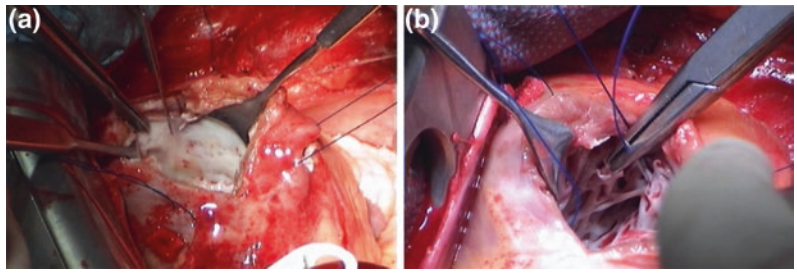

Fig. 11 **a**, **b** LV Aneurysm with fibrosis on septal area and the Dor recalibration stitch

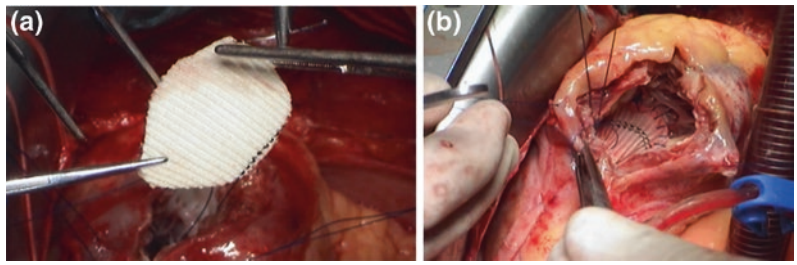

Fig. 12 **a**, **b** LV aneurysm repair with Dacron patch inserted in the LV cavity for geometric reconstruction Dor procedure

by various factors such as tumors (bronchopulmonary cancer, lymphomas, germinal tumors, sarcomas) [42], thymoma, genetic abnormalities [43], fistulas [44], increased venous pressure, superior vena cava thrombosis, cardiac diseases as tricuspid diseases, tumors [45], pericarditis, emphysema bubble [46], etc.

Drainage of pulmonary veins into the superior vena cava instead left pulmonary veins as shown in the sinus venosus atrial septal defect are a common cause of superior vena cava dilatation. The persistence of the left superior vena cava can be radiologically seen by CT and MRI and is usually is drained in coronary sinus [47].

Surgical treatment of superior vena cava aneurysms needs cardiopulmonary bypass, superior vena cava resection and right atrial reimplantation.

Innominate veins aneurysms are rare, about 20 cases in literature [48]. The radiological appearance is as a double contour of the aortic arch mimicking coarctation. Etiology is multifactorial as congenital, inflammations, tumors, etc.

There is a risk of thrombosis and surgery is suitable for saccular aneurysms. The approach is median sternotomy and aneurysm resection can be done without cardiopulmonary bypass [49]. It is recommended in the case of voluminous aneurysms with wide implantation pedicle.

Azygos vein aneurysms are infrequent, around 30 cases have been described in literature. Etiology may be congenital, or due to increase in venous pressure as portal hypertension, posttraumatic, tumor or idiopathic hypertension [50]. It is usually an accidental discovery on chest X-ray. CT and MRI are needed for diagnosis. They can occur as spindle or saccular aneurysm where the last is bulky and could be symptomatic. Fusiform aneurysms tend to remain unchanged in size and usually do not need surgical treatment. There is minor risk of thrombosis and pulmonary embolism [51].

Surgical management consists of aneurysmal excision through the VATS procedure. Angiography is used because visualizes the fistulous course.

Constrictive pericarditis
It is caused by a rigid pericardium that restricts cardiac chamber movements. Clinical signs are heart failure with dyspnea on exertion, edema, arrhythmias. Diagnostic criteria include dissociation of intracardiac and intrathoracic pressures and enhanced ventricular interaction.

Etiology could be tuberculosis or idiopathic. Infection, malignancy, radiation therapy or rheumatic disease are other causes of acute pericarditis.

Chest X-ray could show pericardial calcifications that are suggestive for diagnosis. Mayo criteria for echocardiography diagnosis are respiration-related ventricular septal shift, preserved or increased medial mitral e' velocity, and prominent hepatic vein expiratory diastolic flow reversal.

CT can assess the pericardial thickness and calcifications.

The treatment is medical with anti-inflammatory therapy, antibiotic therapy for tuberculosis and surgical treatment pericardiectomy which has a mortality between 6 and 7% [52].

Double aortic arch (Figs. 13 and 14) is a rare congenital anomaly of the aorta which consists on persistence of both dorsal aortae which form a complete/incomplete vascular ring with compressive tracheal and esophageal syndrome [53]. Clinical signs are nonspecific, dyspnea, cough, apnea, and persistent dysphagia are common. The diagnosis could be done early in life or in adult stage. Both aortic arches might be permeable, or one could be atretic. Usually is a permeable right aortic arch with left arch which is atretic. It could be associated with

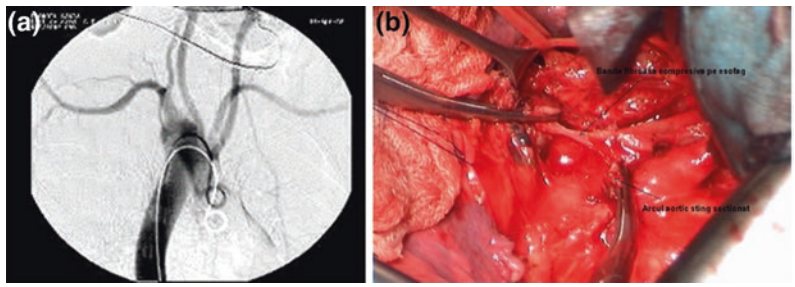

Fig. 13 **a**, **b** Double aortic arch with right arch permeable and atretic left aortic arch and persistent ductus arteriosus

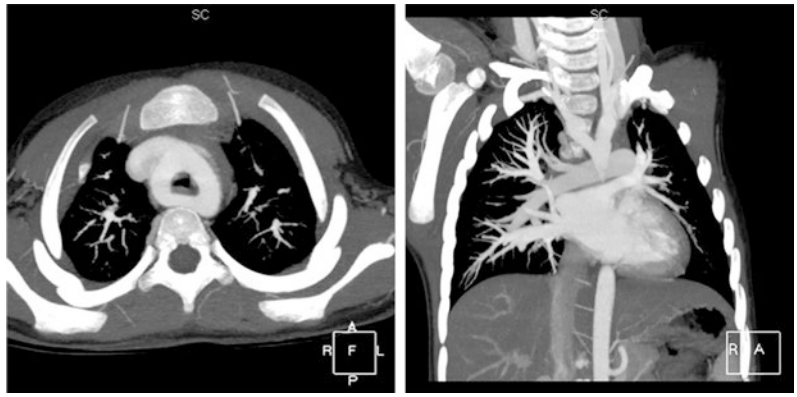

Fig. 14 Contrast-enhanced CT showing the double aortic arch From [53]. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited

aortic coarctation and ductus arteriosus which should be included in the repair (divided and ligated).

The arch branches could have anomalous origin (as retroesophageal right subclavian artery) from the arterial ring or left pulmonary artery could arise from the right pulmonary artery [54]. Other congenital heart anomalies may be also present.

Bronchoscopy shows tracheal compression; barium swallow study reveals an esophageal indentation caused by the vascular ring. 3D computed tomography angiography and cardiac magnetic resonance are important in describing the anatomy and precise diagnose of the anomaly. Surgical approaches are median sternotomy, left thoracotomy or VATS.

Because some of the components of double aortic arch are atretic (non-circulated by blood), surgical disconnection or ligation is usually enough for releasing the trachea and esophagus from the constrictive ring. Sometimes might be necessary disconnection and reimplantation of one of the arch branches and ductus arteriosus division. Postoperative outcome is good with low mortality in the absence of other major cardiac anomalies.

Systemic-to-pulmonary arteriovenous fistulas can be congenital or acquired. Congenital ones occur in 15% of cases [55] and are associated with heart anomalies. Usually occur after inflammation or after thoracic surgery [56] or cardiac surgery. Usually the symptoms are hemoptysis, cyanosis and dyspnea.

Echocardiography shows pulmonary hypertension. Embolization or surgery are both therapeutic [57].

Supreme intercostal vein aneurysm is infrequent. This vein drains the venous blood from of two, three and four intercostal tributaries. It may appear as a protuberant opacity in the aorta. When it occurs, it is due to obstruction of the cave vein, Budd-Chiari syndrome or other congenital causes.

Anomalous pulmonary venous drainage return is partially or total. Routinely the upper right pulmonary veins are drained in SVC or into right atrium and are accompanied by the rule of interatrial septal defect type sinus venous. The partial pulmonary venous drainage abnormalities of the left veins are rare.

The total anomalous pulmonary venous return (TAPVR) has next types supracardiac TAPVR, cardiac TAPVR, infracardiac TAPVR, mixed TAPVR. In supracardiac TAPVR the right and left pulmonary veins are drained by a vertical vein that flows into the left innominate vein and radiologically the heart silhouette arises like a snowman shape.

The diagnosis is made by angiography, CT and MRI. Total anomalous pulmonary vein return (TAPVR) needs surgery in the first year of life, but partially anomalous return is tolerated better and could be addressed to surgery at any time. Pulmonary hypertension develops with no indication for surgery [58].

Pulmonary veins aneurysms are rare and can be congenital or acquired after cardiac procedures [59] and clinically are manifest as perihilar right and left opacities. Symptoms are nonspecific as chest pain and dyspnea. The diagnosis is made by 3D multi-slice computed tomography. Usually it does not need treatment unless complications arise like thrombosis or rupture.

Esophageal Lesions

There are several esophageal lesions that can mimic the appearance of mediastinum tumors as achalasia, large diverticula, or the esophageal malformations (esophageal duplication).

Differential diagnosis with mediastinal tumors is reached through the routine examinations of the esophagus: barium X-ray and manometry.

Lung Lesions

Bronchial lung cancer

Anatomy

Pulmonary tumors with paramediastinal, mediastinum, and central hilum localizations, can be detected on standard chest X-ray like mediastinal tumors (enlarged mediastinum). Lung cancer

may invade mediastinum, either by contiguity (direct tumor invasion), or by lymph nodes metastases, generating both radiological clinical appearance of a mediastinal syndrome. In this category, small cell lung carcinoma is the most common cause of superior vena cava syndrome.

Clinical Examination
Lung cancers are asymptomatic for a long time. Hemoptysis is the most frequent sign at presentation. The hoarseness, the change in the cough character to a chronic bronchitis raises the suspicion of a lung cancer that causes the invasion of the mediastinum and the left recurrent larynx nerve. Progressive stress dyspnea, recurrent pulmonary infections and endobronchial obstruction with secondary pulmonary atelectasis are often seen. Chest pain marks the stage of parietal invasion. Shoulder pain, irradiated on the internal side of the manubrium accompanied by Claude-Bernard-Horner syndrome (myosis, enophthalmia, palpebral ptosis) raises the suspicion of a tumor of the pulmonary apex that produces the invasion of the upper thoracic aperture (Pancoast tumor). Weight loss, inappetence, suggests neoplastic impregnation. Migratory joint pain or recurrent thrombophlebitis are paraneoplastic signs that may precede the radiological occurrence of the pulmonary tumor.

Chest X-ray
It can be negative by overlapping the pulmonary tumor opacity over the mediastinal shade.

CT Contrast Exam
It supplies important information about tumor location, consistency, invasion sites, locoregional spread (the presence of hilar and mediastinal adenopathy) and metastases (brain, bones, adrenal, liver).

CT diagnostic criteria for mediastinal invasion [18]:

1. Contiguous mediastinal mass with a lung tumor, leading to mediastinal vessels or esophagus compression or replacing the mediastinal fat with soft tissue.
2. Obliteration of the normal fat layer neighboring mediastinal vessels.
3. Tumor contact around 1/4 the aortic wall circumference.
4. Tumor contact with more than 3 cm of mediastinum.

MRI
More sensitive than CT exam in mediastinal invasion assessing [18]:

1. Systemic vessels (upper cavity vein, brahiocephalic venous trunk): identifies the degree of venous obstruction, the presence of a possible intraluminal tumor.
2. Pericardium and heart: atrial tumor invasion, a cardiac cavity distortion.
3. The permeability of the pulmonary veins and presence of tumor invasion in the left atrial appendage.
4. Posterior structures of the visceral mediastinum: aorta and esophagus.
5. Costal vertebral grooves: soft parts, conjugation holes, intramedullary invasion.

Bronchoscopy
Very sensitive for endobronchial invasion. Bronchoscopic semiology of endobronchial cancer may include:

1. Tumor signs: endobronchial vegetation, bronchial stenosis.
2. Indirect tumor signs: alterations in bronchial dynamics, extrinsic compressions, anatomical changes of the bronchial shift.
3. Signs of lymph nodes metastases: compressions in the bronchial walls or bronchiectasis.

Hydatic Lung Cyst

Anatomy
The hydatic lung cyst developed in the lung, which bombes towards the mediastinum, can raise differential diagnostic problems with mediastinum tumors due to the similar appearance on standard radiography (Fig. 15) [60].

Clinical exam
In the uncomplicated hydatic cyst clinical manifestations are absent in over 80% of cases. When

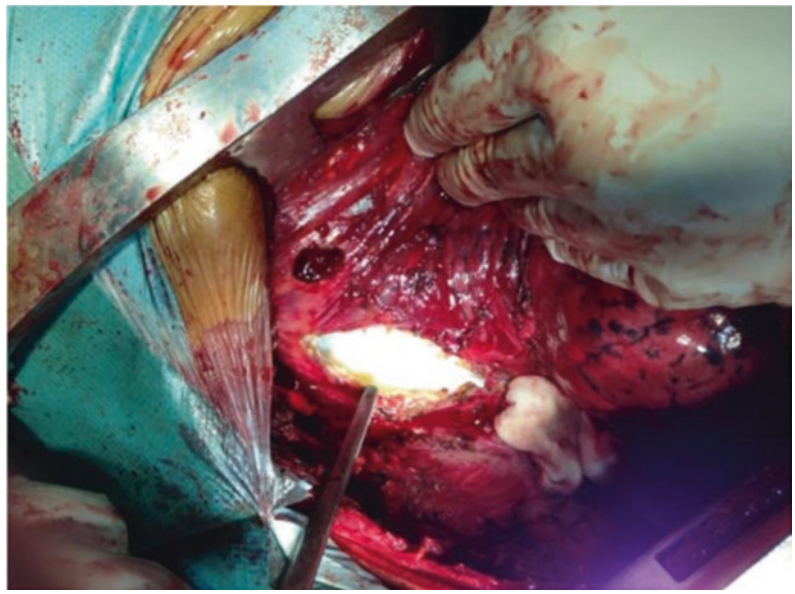

Fig. 15 Image taken intraoperatively objectifying the pericyst and cyst wall (white) From [60]. This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited

present, they are dependent on the size of the cyst and its peripheral or central location. Cough may be dry, excruciating or may be accompanied by expectoration and subfebrile status (may be a clinical sign of eruption). Chest pain, is usually of low intensity, has fixed point, is continuous and progressive, worsened by inspiration and succumb to mild painkillers. Sometimes shortness of effort may be present in giant hydatic cysts. Urticaria with pruritus rarely occurs in the uncomplicated cyst. In percussion, liquid dullness can be found. On auscultation is reached the abolition of the vesicular murmur and more often the bronchial rales or pleural friction are heard. In the large juxtacardiac hydatic cyst, the auscultation of the cyst can perceive the sign of Ostrov: cardiac noises are transmitted through the liquid area of the cyst, being perceptible at the level of the dullness area.

Chest X-ray

The uncomplicated hydatic lung cyst is presented as a round opacity, well-delimited, of subcostal intensity.

CT Examination

It reveals the existence of a round opacity, delimited by the surrounding parenchyma, with liquid density, without mediastinal or hilar adenopathy.

MRI

It finds its usefulness especially in complicated hydatic cyst or alveolar echinococcus.

TTE

Transthoracic echography reveals the transonic character of the formation.

Abdominal ultrasound can detect concomitant presence of cystic lung and liver images, due to the frequent combination of both localizations.

Bronchoscopy

It is especially useful through "negative" data. However, the bronchi can be compressed from the outside and stenosed by cystic formation.

Sputum Examination
Can highlight the presence of hydatic material (membrane, blistering daughters, scolex), which is pathognomonic for the hydatic cyst cracked or broken into the tracheobronchial tree.

Laboratory examinations
Eosinophilia is not specific to the hydatic cyst. Values ranging from 5 to 12% may mean the presence of a parasitosis.

Positive Cassoni intradermic reaction, the reaction of fixation of the Weinberg-PÂRVU complement and the positive ELISA test support the diagnosis of hydatic cyst.

Diaphragmatic Lesions

Hydatic Cyst of the Diaphragm

Anatomy
It is a rare pathogenic entity, localized more often on the right and exceptional on the left side. It is located in full muscular diaphragmatic tissue. Other mandatory conditions for the positive diagnosis: the cyst does not have bile (intraoperative finding) and there is no other localization of hydatic cyst in the vicinity.

Clinical exam
There are sometimes non-specific signs that draw attention to the involvement of phrenic nerve damage: irritative cough, pain in the right hypochondrium irradiated in the shoulder or rebel hiccups.

Chest X-ray
It is presented as a rounded opacity located at the base of the right hemithorax.

CT Exam
Performed with contrast substance does not differentiate from a hepatic localization of the lesion.

MRI
It appreciates better diaphragmatic localization.

Hepatic scintigraphy
It does not show the existence of mixed liver areas.

Congenital Diaphragmatic Cysts

Mesothelial cysts
They are defects in the process of fusion of the pleuro-pericardial and pleuro-peritoneal membranes, occurring in the 6th week of intrauterine life. They are formed by "encasing" a portion of these membranes at the level of the fusion area of the transverse septum.

Bronchogenic cysts
It is formed by sequestration of a bronchial bud in the process of diaphragm development (belongs to extralobar pulmonary sequestrations).

Diaphragm cysts are most commonly asymptomatic, being a random radiological discovery. The diagnosis is only intraoperative.

Diaphragmatic Tumors

Benign diaphragmatic tumors
The most common benign diaphragmatic tumor is diaphragmatic lipoma. The other benign tumors may have mesothelial or neurogenic origin.

Most commonly they are asymptomatic. 50% of the diaphragmatic neurogenic tumors are associated with hypertrophic pulmonary osteoarthropathy (Bamberger-Marie syndrome).

They are a random radiological discovery.

The diagnosis is only intraoperative.

Malignant diaphragmatic tumors
Most of the diaphragmatic malignant tumors have mesenchymal origin (sarcomas).

Generally, are with no symptoms. Lately become bulky tumors that can produce the invasion of neighboring organs and can be clinically manifested by: thoraco-abdominal pain, permanent hiccups, subfebrile state, pleural and digestive signs. It manifests as a

radioopaque voluminous mass, with lower intrathoracic localization. The diagnosis is only intraoperative.

Subdiaphragmatic Lesions

Hiatal hernias

Are permanent or intermittent penetration of the stomach into the thorax, at the level of the visceral mediastinum, through the esophageal hiatus.

Hiatal hernias can be: sliding (type I), paraoesophageal (type II), mixed (type III) (combinations between I and II) and hiatal hernias with organs other than the stomach (type IV) (colon, epiploon, spleen, small intestine) [30].

Sliding hiatal hernias

Are the most frequent hiatal hernias (90-95%) [28]. It appears in the 4th-5th decade of life. It represents the intrathoracic migration of the esophagus-gastric junction. They can be permanent or intermittent.

Clinically about 50% are asymptomatic (accidental radiological discovery) and 50% exhibit symptoms caused by gastroesophageal reflux: dysphagia, pain, regurgitation, dysphonia, pharyngeal paresthesia, chronic nocturnal cough, or symptoms caused by the volume of the hernia: meal paroxysmal dyspnea (compression on the lung), palpitations, angina type pain (heart compression phenomena) or incoercible hiccups (phrenic irritation phenomena).

Radiological Exam with Barium

Performed either upright or in special positions (Trendelenburg or reverse), with or without forced respiratory maneuvers (Valsalva and Muller) show the supradiaphragmatic presence of the cardia of the esophagus, accompanied or not by the presence of gastro-esophageal reflux. In large and fixed hiatal hernias, on orthostatic position, an opaque, round mass can be highlighted, above the left hemidiaphragm with retrocardiac situation.

Endoscopy

It shows the presence of gastro-esophageal reflux in the lower esophagus, confirms the larger opening of the angle of His, assesses the degree of competence of the esophageal cardia and can signal the presence of complications: esophagitis, stenosis, esophageal ulcer, or evolving cancer.

Esophageal manometry

It measures the pressures in the lower and middle esophagus. A pressure less than 10 mm Hg signals an incompetent inferior esophageal sphincter, which generate the gastro-esophageal reflux.

Esophageal scintigraphy

It is a non-invasive test, used in pediatric practice, which accurately measures the esophageal clearance and the gastro-esophageal reflux.

Anterior diaphragmatic hernia (Morgagni-Larrey hernia)

Anatomy

It is based on the existence of an embryological defect of development of septum transversum and failed fusion of sternal and costal elements of the diaphragm. The anatomical defect can vary, from a simple area of weakness to the absence of the sternal portion of the diaphragm (large anterior sternocostal hiatus).

They occur most often in women, on the right side especially and most of the time they have the hernial bag (fetal hernias).

We find most commonly the great omentum or the transverse colon in the hernial bag.

Clinical Examination

About 30–50% of the Morgagny-Larrey hernias are asymptomatic in adults (radiological random finding).

In newborn babies it manifests loudly, through severe respiratory distress. In the most common pediatric population are respiratory manifestations as (pain, cough, dyspnea). In adults, additionally digestive manifestations may

appear: postprandial discomfort, suboclusive manifestations. Rarely, in adults, the signs of gastric volvulus can be installed: severe dyspnea accompanied by high occlusion syndrome signs.

Standard radiological exam
Supradiaphragmatic presence of the epiploon or other digestive segment can be presented like an enlarged mediastinal opacity at radiological examination. The latter can be confirmed by the barium examination (barium meal or enema).

CT Exam
The transversal sections that it performs do not allow a very precise diagnosis of diaphragmatic hernia, being difficult to differentiate the presence of an elevated abdominal viscera or a herniated one. It can be useful by the "collar " sign (constriction of the herniated viscera at the place of passage through the diaphragm).

MRI Exam
It represents the imaging method of election for the investigation of the thoracic wall and diaphragm.

Posterior diaphragmatic hernia (Bochdalek hernia)

Anatomy
It is a congenital diaphragmatic hernia produced by a failure of the posterolateral diaphragmatic foramina to fuse properly. It can be a totally agenesis of the posterolateral part of the diaphragm (embryonic type of hernias), with early herniation in the thorax of the abdominal viscera without a pleuro-peritoneal bag, or a muscular aplasia of the pleuro-peritoneal membrane (fetal type of hernias) with the late herniation in the thorax of the abdominal viscera covered by a pleuro-peritoneal bag.

Among 80% appear on the left side. The size of the defect ranges from 1 to 2 cm to complete absence of hemidiaphragm.

Clinical examination
They are characteristic for the neonatal and childhood period, being rare in adults. It is more prevalent in the boys. It may occur isolated or associated with other congenital malformations: hypoplastic lung, pericardial absence, the complex of the left heart hypoplasia, central nervous system abnormalities, digestive, genito-urinary, musculoskeletal. The acute form occurs at once after birth and it is manifested by the triad: acute respiratory failure, digestive occlusion, displacement of the heart in the right hemithorax. The attenuated form is diagnosed in children who are presenting for respiratory distress and intermittent cyanosis at the effort. Latent (asymptomatic) form is discovered in adulthood by a routine radiography.

Standard radiological Exam
It shows the presence of a digestive segment in the respective hemithorax, confirmed by the barium X-Rays examination of the gastrointestinal tract.

Diaphragmatic relaxation (diaphragmatic eventration)

Anatomy
It is a diaphragmatic muscular hypoplasia. The diaphragm is flaccid, atrophic, as a thin membrane holding rare muscle fibers with degeneration of varying degrees. The phrenic nerve and its branches exhibits some degree of degeneration lesions. As a consequence, presence of the diaphragmatic eventration causes topographical changes of the adjacent organs such as: the heart is pushed to the right and the lung is pushed upwards by the elevated abdominal viscera.

Clinical examination
It is often a random radiological discovery. In severe cases, chest symptoms (pain at the base of the hemithorax, dyspnea, cough) and digestive ones (nausea, dysphagia, constipation) are present.

Standard radiological examination
It highlights the high position of one of the diaphragmatic domes, the ascending of the gastric air bubble and the presence of superior colon images under the diaphragm. Fluoroscopy examination finds the immobility of the involved hemidiaphragm or its paradoxical movements during respiration. The barium X-Rays examination of the gastrointestinal tract shows the high position of the diaphragm.

MRI
It represents the imaging method of election to assess the integrity of the diaphragm.

Pancreatic pseudocyst
It is a complication of acute or chronic pancreatitis. It is formed at the site of pancreatic necrosis and does not have its own walls. Pancreatic pseudocyst usually contain enzymatic fluid and necrotic debris.

It can reach an impressive volume, bulky, compressing the adjacent organs. These gigantic cysts can mimic the appearance of a mediastinal tumor in the standard X-Ray examination [41].

Abdominal ultrasound and CT examinations are the essential diagnostic tools in the assessments of the pancreatic pseudocysts.

Self-study Questionnaire
Question 1

Which of the next sentences about arterial aneurysms are true?

A. Arterial aneurysms are mimicking the mediastinal tumors and are discovered accidentally on radiologic investigation for other medical reasons.
B. Arterial aneurysms are usually secondary to atherosclerosis or because of genetic disorders of connective tissue
C. Mediastinal syndrome could appear because of a large thoracic aortic aneurysm.
D. Ascending aortic aneurysms have always surgical treatment because of the risk of rupture.
E. Descending aortic aneurysms are treated by TEVAR because of higher mortality of open surgery.

Correct answers: A, B, C
The ascending aortic aneurysm diameter are not always for surgery. Surgery must be performed if the aortic diameter is 55 mm or more, exception for genetic disease where the aortic diameter must be 50 mm or association of moderate or severe aortic regurgitation. Descending aortic aneurysms diameter more than 60 mm are for open surgery D, and E, answers are false.

Question 2
Which of the following sentences about left ventricular aneurysms are true?

A. Clinical symptoms are nonspecific and chest pain, shortness of breath or arrythmias are common.
B. Surgical treatment is needed in complicated left ventricular aneurysms
C. Ventricular thrombosis is a contraindication of surgery.
D. Rupture is a common complication in large left ventricular aneurysms.
E. Coronary artery disease is present and needs to be corrected by surgery

Correct answers: A, B, D, E
Intraventricular thrombosis associated with left ventricular aneurysm has a major indication for surgical treatment because of high risk of stroke.

Question 3
Which of the following sentences concerning double aortic arch syndrome are false?

A. Double aortic arch is diagnosed early in life because of life-threatening symptoms
B. Double aortic arch symptoms are specific and clinical diagnosis is typically easy.
C. Surgical treatment is associated with low mortality and good outcome.
D. 3D CT angiography is given the anatomical details for surgical repair.
E. Right aortic arch is usually permeable, and the left is atretic.

Correct answers: A, B
Usually the vascular rings are asymptomatic, then the diagnostic and clinical symptoms are difficult, than false answers are A,B. Surgical treatment is successful and CT and MRI are important for diagnostic details. Right aortic arch usually is permeable and left arch atretic in most of the cases.

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The Pericardium

Embryology and Anatomy of the Pericardium

Davut Cekmecelioglu, Taylan Adademir, and Kaan Kırali

Key Points

1. In the adult, the intraembryonic coelom is splitted into 3 well-defined compartments: the pericardial cavity with the heart, the pleural cavities with the lungs, and the peritoneal cavity with the viscera below the diaphragm.
2. The potential space between the parietal and visceral layers consists of a thin coat of liquid and is known as the pericardial cavity. It normally contains less than 50 ml of serous fluid which human heart is contained in.
3. The transverse pericardial sinus is particularly important to cardiac surgeons. Placing a tying around aorta and pulmonary trunk via transverse sinus can facilitate cardiopulmonary bypass setting and heart manipulation during cardiac surgery.
4. Closing of the pericardial incision following an open cardiac surgery has been suggested to (a) avoid possible postoperative complications, (b) decrease the frequency of ventricular hypertrophy, and (c) ease the future potential reoperations by lessening fibrosis.

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Introduction

The pericardium is something of a mystery. Like the vermiform appendix, we can live well do without it, yet when it becomes sick, because of its strategic position; it turns into a chokehold surround the heart and therefore threatens life itself.

The pericardium is a fibroserous, fluid-filled conical sack that surrounds and encompasses the muscular body of the heart and the roots of the great cardiac vessels as the aorta, pulmonary artery, pulmonary veins, and the superior and inferior vena cavae [1, 2] (Fig. 1). Under normal circumstances, the pericardium separates and isolates the heart from contact of the surrounding tissues, allowing freedom of cardiac movement within the restrains of the pericardial space.

This chapter deals with the structure of the pericardium and will give an outline of the embryological development, anatomical structure, innervations, functions and clinical significance of the pericardium.

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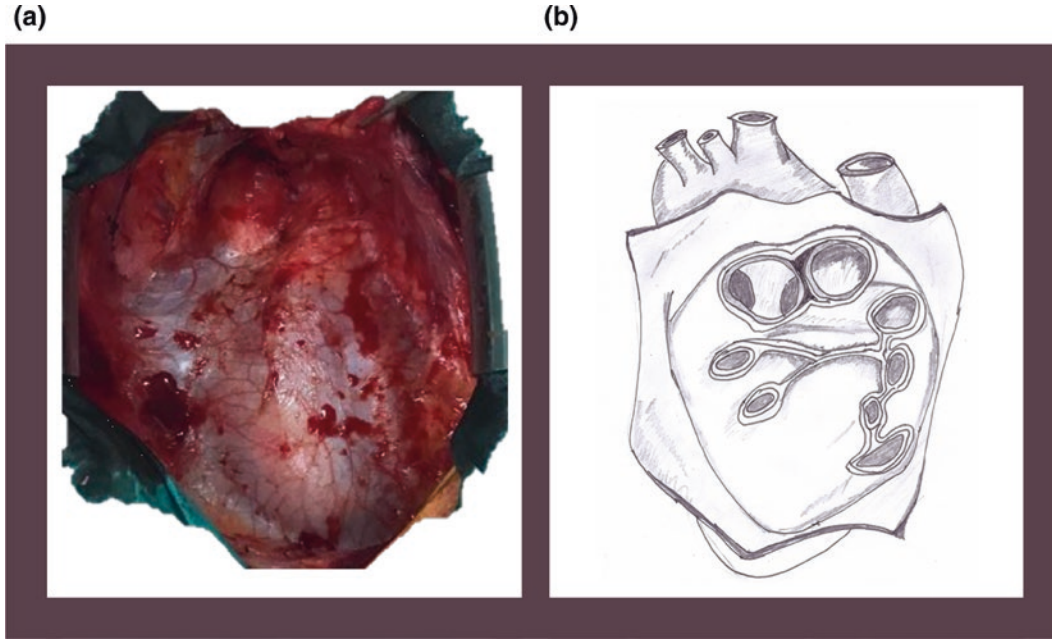

Fig. 1 Pericardium is the fibrous sac that encompass the heart and cardiac vessels; **a** an intraoperative image of anterior pericardium that surround the heart and major vessels, **b** an illustration of posterior pericardium and relationship with major cardiac vessels

Embryological Development of Pericardium

Formation of the Human Body Cavities

During the fourth week of gestation, the sides of the embryo begin to grow ventrally generating two lateral body wall folds. These two folds consist of the parietal layer of lateral plate mesoderm, overlying ectoderm, and cells from adjacent somites that migrate into the mesoderm layer across the lateral somatic border [3]. As these folds develop, the endoderm layer also folds ventrally and closes to form the gut tube. By the end of the fourth week, the lateral body wall folds meet in the mid-line and fuse to close the ventral body wall. This closure is assisted by the growth of the head and tail regions which cause the embryo to curve into the fetal position (Fig. 2).

Somatic mesoderm cells cover the intraembryonic cavity, transform into mesothelial and become the parietal lining of the serous membranes layers the outside of the peritoneal, pleural, and pericardial cavities [3].

i. As the head end of the embryo develops forward and folds off from the yolk sac, the 2 compact chains approach each other ventrally and also acquire a lumen lined by endothelial cells. Thus, the 2 endocardial tubes are formed.
ii. The lumen of each of the 2 tubes slowly expands cranially into the midline cell strands and finally the two meet.
iii. With another lateral folding of the embryo, the fusion of the 2 endocardial tubes then develops from the cephalic point in a caudal focus, thus forming a single endocardial tube [3, 4].

At the same time, with lateral folding and the medial migration and fusion of the tubes, the intracoelomic cavities, right and left, also approach each other in the midline. Ab initio, at the 4 somite state which occurs around day 21,

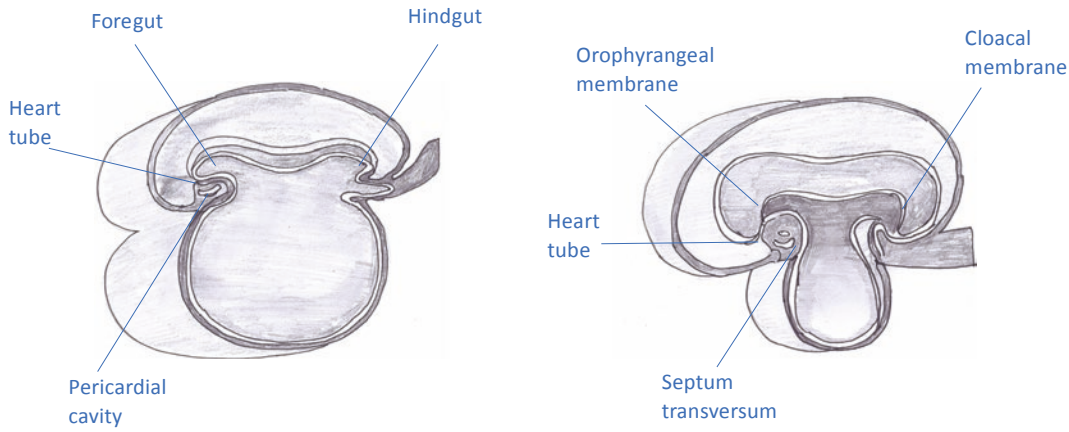

Fig. 2 Midsagittal sections of embryos at various stages of development showing cephalocaudal folding and its effects upon position of the heart, septum transversum

the primitive heart tubes are attached to the anterior and posterior walls, between the right and left coelomic cavities, by the dorsal and ventral mesocardium.

i. While the ventral part vanishes just after its early formation, the dorsal mesocardium remains a little longer.
ii. Whereas the heart tube elongates, curves, and loops, it gradually submerges into the dorsal wall of the pericardial cavity, which is formed from a fusion of the right and left intraembryonic coelomic cavities.
iii. Finally, beginning at the cranial end, the dorsal mesocardium also breaks down and has completely disappeared at the 16-somite stage; and the heart tube is then freely held up in the pericardial cavity and is connected to the surrounding tissues only at its cephalic and caudal ends [3]. The newly developed channel, dorsal to the primitive heart tube, is the futurity of transverse sinus of the pericardial cavity (Fig. 3).

Thoracic Cavity

In week 5, the intraembryonic coelom comprises of thoracic and abdominal parts, linked by a canal found on each side of the foregut. In the adult, the intraembryonic coelom is splitted into 3 well-defined compartments: the pericardial cavity with the heart, the pleural cavities with the lungs, and the peritoneal cavity with the viscera below the diaphragm. The diaphragm forms the septum transversum between the thorax and abdomen; the pleuropericardial membrane forms between the pericardial and pleural cavities.

The septum transversum is a thick plate of mesodermal tissue occupying the space between the thoracic cavity and the stem of the yolk sac (Figs. 2 and 3). This septum does not divide the thoracic and abdominal cavities entirely but remains large openings, the pericardioperitoneal canals, on each side of the foregut.

When lung buds start to grow, they enlarge caudolaterally within the pericardioperitoneal canals. As a result of the rapid development of the lungs, the pericardioperitoneal canals become too small, and the lungs begin to expand into the mesenchyme of the body wall dorsally, laterally, and ventrally and lateral the expansion is posterior to the pleuropericardial folds. With expansion of the lungs, the mesoderm of the body wall divides into two parts [4, 5] (Fig. 4); the final wall of the thorax and the pleuropericardial membranes, which are extensions of the pleuropericardial creases that consist the common phrenic nerves and cardinal veins. Subsequently, they merge with each other and with the base of the lungs, and the thoracic cavity is splitted up into the final pericardial cavity and two pleural

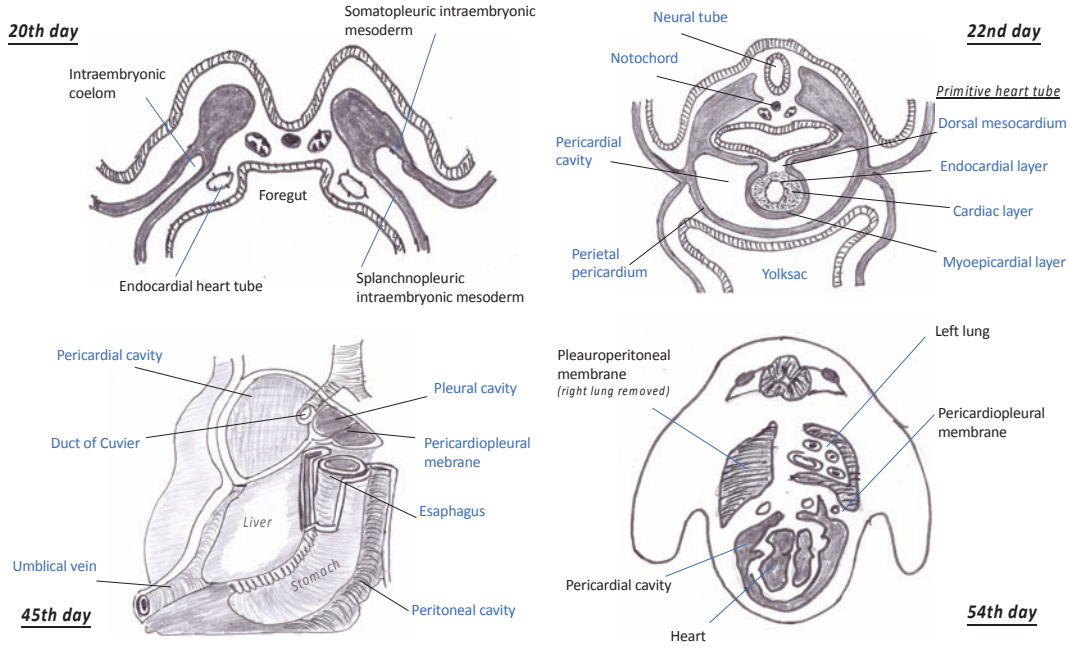

Fig. 3 Development of pericardial, pleural and peritoneal cavities

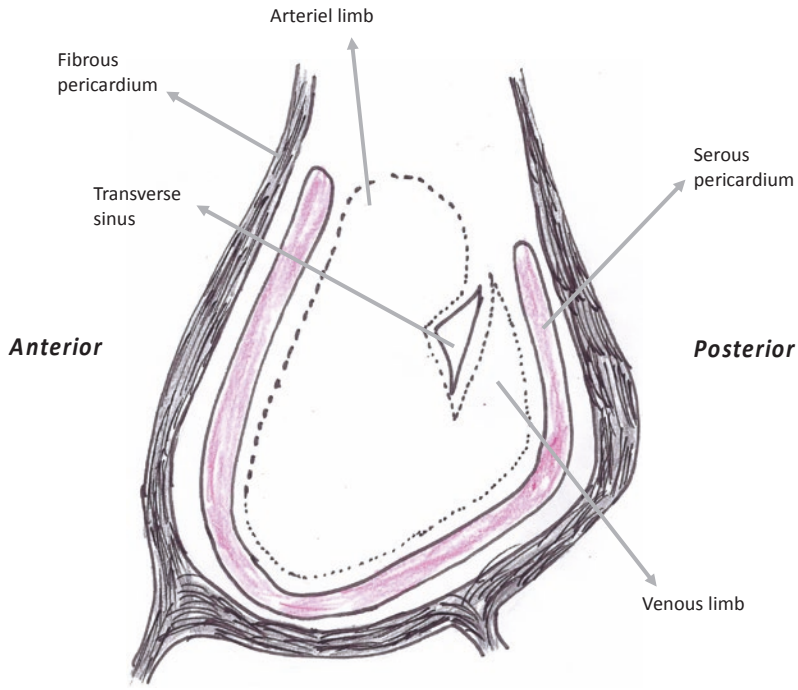

Fig. 4 Schematic sagittal section through the heart and pericardium. Note that the reflections of the pericardium

cavities. The pleuropericardial membranes constitute the fibrous pericardium in the adult.

Congenital defects of the pericardium are rare [5]. A total absence of the pericardium is rarely symptomatic. Usually, the congenital pericardial failure is not recognized until surgical exploration or postmortem investigation is conducted [6].

Anatomical Structure of Pericardium

In humans, the 1 to 3 mm thick fibrous pericardium develops a flask-shaped bag. The **pericardium** is a fibroserous membrane that overlies the heart and the root of its great vessels [1, 2, 7]. The neck of the pericardium on superior aspect is closed by its extensions surrounding the great cardiac vessels; the base is attached to the central tendon and to the muscular fibers of the left side of the diaphragm. Great portion of the diaphragmatic connection of the pericardium has loose fibrous tissue that can be easily detached, but there is a small section over the central tendon where the diaphragm and the pericardium are entirely merged.

Assessment of the pericardium shows that it consists of two interconnected different and isolated anatomical structures (Fig. 4). The outer sac is known as the fibrous pericardium and has fibrous tissue. The inner sac is known as the serous pericardium and is a delicate membrane resting on loose connective tissue that lies within the fibrous pericardium, lining its inner walls. The heart penetrates the wall of the serous sack from above and behind, forming an infold surrounding nearly the whole pericardial cavity [7, 8].

Fibrous Pericardium

The **fibrous pericardium (FP)** is the outermost layer, and it is firmly bound to the central tendon of the diaphragm. Extrapericardial adipose tissue, is usually found in the corners between the pericardium and diaphragm on both side, and can be identifiable radiographically [9]. The FP defends the heart against brisk overfilling since it is persistent and nearly associated with the great vessels that penetrate it superiorly. The pericardium is connected to the sternum by the sternopericardial ligaments and is disciple to the mediastinal pleura except where the two are divided by the phrenic nerves.

The fibrous pericardium is originated from connective tissue cells, collagen fibers, small elastic fibers, lymphatics and microvasculature. The epicardial layer is composed of connective tissue as well as neural elements and blood vessels [10]. Coarse collagenous bundles in the epipericardial layer compose the sternopericardial ligaments. Mast cells, lymphocytes and histiocytes may be located in each of the fibrosal and epipericardial stratums. The diversed arrangement and the wave like orientation of the collagen fibers in the fibrous stratum are such that they permit for some degree of multidirectional stretch. However, given the inextensible nature of collagen fibrils, once the collagen fibrils are straightened out, other stretching of the fibrous layer is limited. It has also been shown that the waviness of the pericardial collagen is maximal in young adulthood and decreases thereafter with age [11].

The fibrous pericardium continuous superiorly with the tunica adventitia of the great vessels entering and leaving the heart and with the pretracheal layer of deep cervical fascia. It attached anteriorly to the posterior surface of the sternum by the sternopericardial ligaments, which are highly variable in their development. The FP bound posteriorly by loose connective tissue to structures in the posterior mediastinum and continuous inferiorly with the central tendon of the diaphragm.

Serous Pericardium

The internal layer of the FP is lined with a glistening **serous membrane**, the *parietal layer of serous pericardium* [9, 11]. This surface is mirrored onto the heart at the great vessels "aorta, pulmonary trunk and veins, and superior and inferior venae cavae" as the *visceral layer of serous pericardium* (Fig. 4).

The serous pericardium is composed mainly of mesothelium, a single layer of flattened cells forming an epithelium that lines both the internal surface of the fibrous pericardium and the external surface of the heart. Flattened mesothelial cells those luminal layer is entirely lined with surface microvilli and few cilia that are considered to serve as both specialized friction-bearing surfaces also to widen the cell surface area available for fluid transport [10]. Histologic examination of the serousal pericardium suggests the capability of the luminal surface to modify its configuration as well as the ability to permit both transport through intercellular spaces and across the cytoplasm by vesicular transport [12].

The potential space between the parietal and visceral layers consists of a thin coat of liquid and is known as the **pericardial cavity**. It normally contains less than 50 ml of serous fluid which in normal hearts is contained in the pericardial recesses and sinuses mostly over the atrioventricular and interventricular grooves that allows the heart to move and beat in a frictionless setting.

The pericardium is affected by motions of the heart and great vessels, diaphragm and the sternum. Between the left pulmonary artery and subjacent pulmonary vein is a triangular crease of the serous pericardium named as the *ligament of the left vena cava* (rudimentary fold of Marshall). It is made up by a serous stratum over the fragment of the lower part of the left superior vena cava (duct of Cuvier), that regresses during fetal life, but persists as a fibrous band stretching from the highest left intercostal vein to the left atrium, where it lines up with a small vein named as the *vein of the left atrium* (oblique vein of Marshall), ultimately opening into the coronary sinus [13]. The inferior wall (floor) of the fibrous pericardial sac is tightly attached and confluent (partially blended) centrally with the central tendon of the diaphragm. The site of continuity has been known as *the pericardiacophrenic ligament*; which firmly inchor the pericardium and maintains the alignment of the heart within the thorax. Regardless, the FP and central tendon are not two separate structures that merged together secondarily, nor are they separable by dissection. As a result of the attachments just explained, the heart is somewhat well secured in place inside this fibrous sac.

Pericardial Sinuses and Reflections

The visceral stratum (layer) of serous pericardium forms the epicardium, the outmost of three layers of the heart wall. It expands onto the origination of the great vessels, continuous with the parietal layer of serous pericardium. This reflection creates two invaginations one is where the aorta and pulmonary trunk leave the heart and the other where the SVC, IVC, and pulmonary veins enter the heart [9–12].

The ***transverse pericardial sinus*** lies between these two groups of vessels and the reflections of serous pericardium around them, and the reflection of the serous pericardium around the second group of vessels defines the ***oblique pericardial sinus***. The pericardial sinuses form during the development of the heart as a consequence of the folding of the primordial heart tube. As the heart tube folds, its venous end moves posterosuperiorly (Fig. 1) so that the venous end of the tube lies adjacent to the arterial end, separated only by the transverse pericardial sinus, a transversely running passage in the pericardial sac between the origins of the afferent and the efferent great vessels (Fig. 5). Thus the transverse sinus is posterior to the intrapericardial parts of the pulmonary trunk and ascending aorta and anterior to the SVC and superior to the atria of the heart. The ***superior sinus*** or ***superior aortic recess*** extends upon the right portion of the ascending aorta to the beginning of the innominate artery [12]. The superior sinus also joins the transverse sinus behind the aorta, and they are both continually fused until they reach the aortic root.

As the veins of the heart develop and expand, a pericardial reflection surrounding them forms the oblique pericardial sinus, a wide pocket-like recess in the pericardial cavity posterior to the base (posterior aspect) of the heart, formed

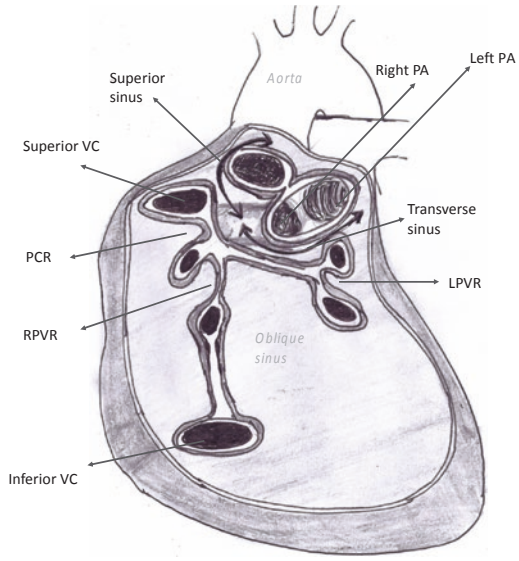

Fig. 5 The anatomy of the pericardium and its reflections along the great vessels, sinuses, and recesses are shown in an anterior view after removing the heart. PA: pulmonary artery, VC: vena cava, PCR: postcaval recess, RPVR: right pulmonary vein recesses, LPVR: left pulmonary vein recesses

by the left atrium (Fig. 5). The oblique sinus is bounded laterally by the pericardial reflections surrounding the pulmonary veins and IVC and posteriorly by the pericardium overlying the anterior aspect of the esophagus. The oblique sinus can be entered inferiorly and will admit several fingers; however, they cannot pass around any of these structures because the sinus is a blind sac(cul-de-sac).

Clinical Importance of the Transverse Pericardial Sinus

The transverse pericardial sinus is particularly important to cardiac surgeons [13]. After the pericardial sac is opened anteriorly, a tying can be passed through the transverse pericardial sinus posterior to the aorta and pulmonary trunk (Fig. 6). This facilitates placing surgical clamps, inserting cannulas for cardiopulmonary bypass, conducting cardiac surgery and etc.

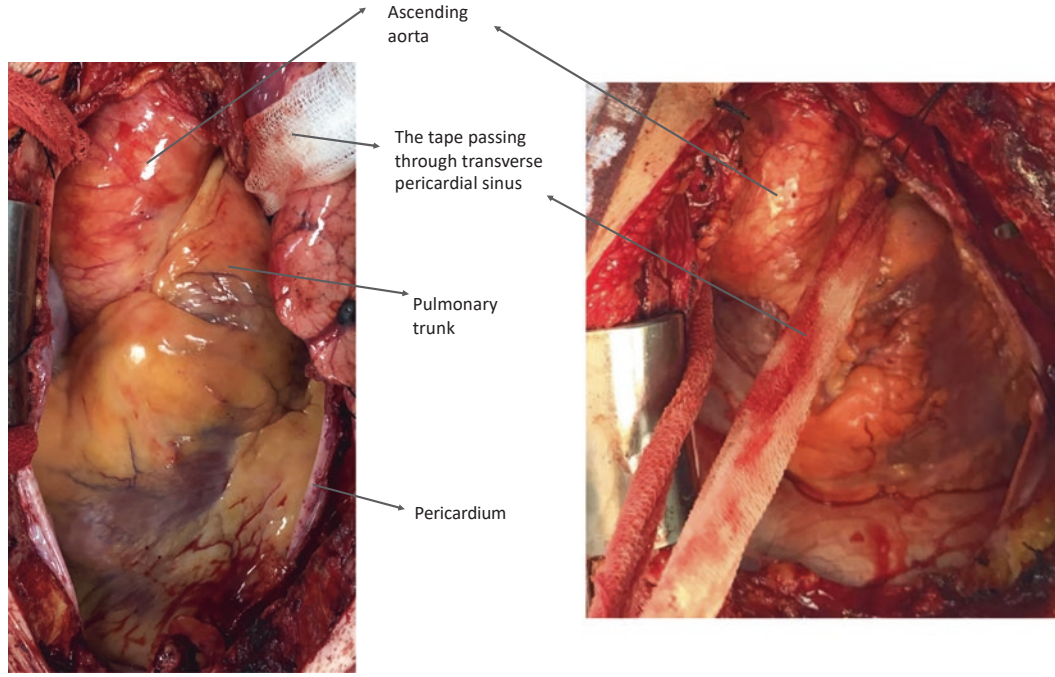

Fig. 6 Intraoperative images from an open heart surgery showed the tape passing through transverse pericardial sinus

Blood Supply and Innervation of the Pericardium

The arterial supply of the pericardium is mainly from a slight branch of the internal thoracic artery, the pericardiacophrenic artery, that often accompanies or at least parallels the phrenic nerve to the diaphragm (Fig. 7). Smaller contributions of blood come from the: musculophrenic artery, a terminal branch of the internal thoracic artery; bronchial, esophageal, and superior phrenic arteries, branches of the thoracic aorta; and coronary arteries (visceral layer of serous pericardium only), the first branches of the aorta [9, 11].

The venous drainage of the pericardium is from the: pericardiacophrenic veins, tributaries of the brachiocephalic (or internal thoracic) veins and also there are variable tributaries of the azygos venous system.

The innervation of the pericardium is from the phrenic nerves (C3–C5), primary source of sensory fibers; pain feelingtransmitted by these nerves are generally referred to the skin (C3–C5 dermatomes) of the ipsilateral supraclavicular region. There is also effect of vagus nerve on pericardium with undefined function. Lastly, the vasomotor nerve supply of the pericardium is conveyed by sympathetic trunks [1, 2].

The innervation of the pericardium by the phrenic nerves (they are somatic not visceral nerves, despite their location) and the course of these somatic nerves between the heart and the lungs make little sense unless the development of the fibrous pericardium is considered. It is split or separated from the developing body wall by the developing pleural cavities, which extend to accommodate the rapidly growing lungs. The lungs develop within the pericardioperitoneal canals that run on both sides of the foregut,

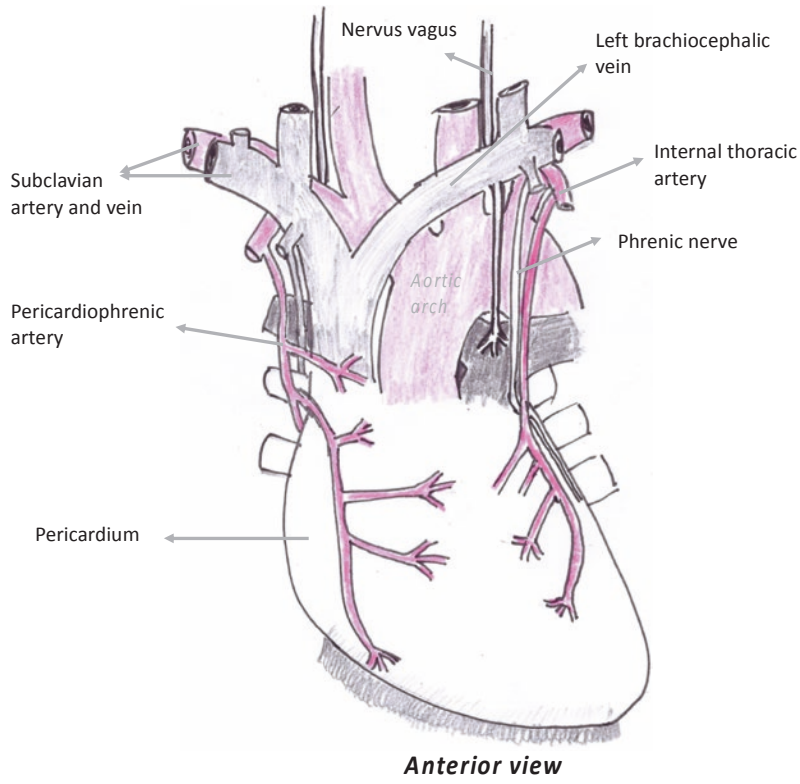

Fig. 7 Blood supply and innervation of the pericardium

connecting the thoracic and abdominal cavities on each side of the septum transversum.

The canals (primordial pleural cavities) are too small to accommodate the rapid growth of the lungs, and they begin to invade the mesenchyme of the body wall posteriorly, laterally, and anteriorly, splitting it into two layers: an outer layer that becomes the definitive thoracic wall (ribs and intercostal muscles) and an inner or deep layer (the pleuropericardial membranes) that contains the phrenic nerves and form the fibrous pericardium [7]. Thus the pericardial sac can be a source of pain just as the rib cage or parietal pleura can be, although that pain tends to be referred to dermatomes of the body wall areas from which we more commonly receive sensation.

Functions of the Pericardium

The grade of the pericardium impact on wall movement depends on the proportion of cardiac to pericardial size, loading circumstances, and the level of the active and passive filling. The presence of the pericardium physically constrains the heart, often resulting in a depressive hemodynamic influence that limits cardiac output by restraining diastolic ventricular filling [14].

The impact of the pericardium on mechanical measures of cardiac performance is usually not clear until ventricular and atrial filling restrictions are reached, for example altering geometrical and mechanical characteristics through causes such as maximum chamber volumes and elasticity. These issues become more evident as these pericardial restrictions become prolonged [7–9].

In particular cases when the restrictive role of the pericardium extensively increases, such as during '*cardiac tamponade*', an increased intrapericardial fluid volume may arise in crucial restriction by the pericardium, that then clinically diminishes cardiac performance [8, 9, 12].

Closing of the pericardial incision following to an open cardiac surgery has been suggested to (a) avoid possible postoperative complications, (b) decrease the frequency of ventricular hypertrophy, and (c) ease the future potential reoperations by lessening fibrosis. Differences in ventricular performance depend on the presence of the pericardium have been reported following cardiac surgery [2, 7].

In summary, the pericardium is a unique structure that surrounds the heart and serves several important physiological functional roles. Removal of the pericardium or increase of fluids within this sac will change hemodynamic performance.

Self-study

1. Which of the following is not a function of the pericardium?
   a. It holds the heart in place.
   b. It acts as a barrier to infections.
   c. It lubricates the outer heat wall.
   d. ***It regulates the temperature of the heart***.
   e. It helps prevent heart overexpansion.

2. Which of the following best describes the location where the two layers of serous pericardium join?
   a. They join above the atria of the heart.
   b. They join at the apex of the heart, above the diaphragm.
   c. ***They join at the base of the heart, where the major blood vessels attach.***
   d. They do not join to each other.

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Constrictive Pericarditis

Ozge Altas, Deniz Gunay, and Kaan Kırali

Abbreviations

CP	Constrictive Pericarditis
CO	Cardiac Output
PCWP	Pulmonary Capillary Wedge Pressure
RA	Right Atrium
LV	Left Ventricle
RV	Right Ventricle
JVP	Jugular Venous Pressure
ECG	Electrocardiography
AFR	Atrial Fibrillation
CT	Computerized Tomography
MRI	Magnetic Resonans Imaging
RC	Restrictive Cardiomyopathy
LVEDP	Left Ventricle End-diastolic Pressure
NSAID	Non-steroid Anti-inflammatory Drug
CPB	Cardiopulmonary Bypass
TI	Tricuspid Insufficiency
NYHA	New York Heart Association
TEE	Trans Esophageal Echocardiography
LCOS	Low Cardiac Output Syndrome
IABP	Intraaortic Balloon Pump
LVEF	Left Ventricle Ejection Fraction

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Key Points

- Pericardiectomy is the only effective treatment for symptomatic CP patients, and complete pericardiectomy remains the potential cure in most patients.
- Intraoperative TEE must be used to assess cardiac recovery as well as obtain any residual atrioventricular valve failure after releasing the inflammatory adhesions.
- The etiology and severity of the disease and the comorbid features influence the degree of recovery after surgery.
- Early intervention must be taken into account as soon as possible to improve survival.

Introduction

Constrictive pericarditis is a disorder of all cardiac chambers' filling due to inelastic, noncompliant pericardium. There was a significant change in the etiology of disease in time. Worldwide, idiopathic constriction in which a cause cannot be identified and is attributed to post-viral infection is considered to be the main cause of 60–80% of all cases in developed countries. Not surprisingly, tuberculosis is still the cause in developing nations and the incidence is almost 50% of patients even though anti-tubercular therapy was given [1, 2]. Most common etiologies of CP can be seen in Table 1. But currently, increasing numbers of

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Table 1 Etiologies of constrictive pericarditis

Infectious	* Post-viral * Post-bacterial * Tuberculosis * Fungus
Malignant	* Metastatic
Inflammatory	* Post-pericardiotomy syndrome * Post-MI (Dressler syndrome) * Post-trauma * Rheumatoid Arthritis
Collagen vascular	* SLE
Others	* Post-radiation * Uremia

patients apply with constriction that has a history of previous cardiac surgery or as a complication of chest irradiation [3–5]. Thus, this etiological switch can be explained by the increased number of surgical interventions expressed the advances in medicine and technology. Additionally, advances in diagnosis with improved expertise of cardiologists may also affect this change [6, 7].

The pericardium is normally <2 cm thick composed of elastin and collagen [8]. CP results in a consequence of chronic inflammatory process of both layers (the serous and parietal). 1.8% of cases following an episode of acute pericarditis develop chronic CP [9]. The incidence of symptomatic CP was low in patients undergoing cardiac surgery among other etiologies with rates of 0.2–2.4% [10, 11]. Generally, pericardium of CP is thickened and calcified, however it may present with normal thickness in almost 18% of cases [12]. Stiffened pericardium following to an inflammatory process limits diastolic filling and the constriction upon the contracting myocardium reduces ventricular function [13]. Early diastolic filling is not affected, however end-diastolic volume, stroke volume and CO decrease respectively. The changes in intra-thoracic pressure during inspiration are not conducted to the heart unlike in cardiac tamponade which is one of a distinguish features of CP. The pressures of all atrium and ventricles are same for both disorders. Distinctively, in cardiac tamponade the pressure decreases with inspiration, whereas in CP PCWP decreases while RA pressure remains constant. In this circumstance, the interventricular septum bulges towards LV showing an impaired mid- and late ventricular filling, because LV volume gets lower than on the RV during deep inspiration. Also, RV cannot expand during inspiration against increased venous return. The accommodation for extra volume can be achieved by ventricular shifting into LV, which is called the principle of enhanced ventricular interaction [14].

The loss of negative intra-thoracic pressure leads a greater decrease in pulmonary veins rather than left heart chambers, so that left heart filling and PCWP decrease which is called dissociation of intra-thoracic and intra-cardiac pressures [14]. This happens because intra-cardiac pressure cannot change during inspiration as the same degree as intra-pleural pressure.

Clinic and Diagnosis

The symptoms are either caused by impaired CO, like dyspnea on exertion or gastrointestinal problems, or associated with volume overload/elevated venous pressure such as ascites, peripheral edema, hepatomegaly. Also, chest pain is generally intense and aggravated by deep breathing.

On physical examination, JVP is generally high, and does not decrease with inspiration, which is known as Kussmaul's sign. However this sign is also an alert for tricuspid valve disease and right heart failure. Cardiac auscultation may reveal a diastolic 'pericardial knock' sound (abnormal S3) by sudden deceleration of ventricular filling.

Initial evaluation must include an ECG, laboratory assessment, chest radiography and echocardiogram. AFR can be present in almost 20–40% of patients [5, 15, 16]. In addition to pericardial calcification, which can be present in one-fourth of patients [16], pulmonary vascular congestion and cardiomegaly might be seen in chest radiography. Being used properly, echocardiogram is sufficient for exclusion of other forms of heart failure. It is already stated that the motion of ventricular septum [17], variation

in hepatic vein [14] and in the mitral inflow velocity [7, 14, 18], and tissue doppler profile of mitral annular velocities were the initials that we should be focusing on. These findings were assessed in one of the largest study where patients were surgically confirmed and which was a blinded comparison of constriction versus restriction or severe tricuspid regurgitation [7]. They concluded with three important findings as echocardiographic criteria: (1) respiration related septal shift, (2) preserved or increased medial mitral é velocity (>9 cm/s), and (3) prominent hepatic vein expiratory diastolic flow reversal ratio (>0.79).

A diagnostic algorithm by echocardiography of CP was suggested at Mayo Clinic, and can be seen in Fig. 1. Myocardial strain imaging can be useful in diagnosis hence CP is associated with preserved longitudinal strain and reduced lateral strain [19]. One important point is that assessment of respiratory changes during echocardiography must be performed if the patient is in sinus rhythm. Atrial fibrillation may corrupt the results.

Particularly for the patients considering surgical intervention, CT scan and cardiac MRI can be performed to detect pericardial calcifications and deformation of ventricular contour. CT scan can reveal calcifications better than MRI; however, MRI offers more about cardiac anatomy and pericardial-myocardial adherence, presence of pericardial effusion and inflammatory process. It is easier to decide the treatment modality by defining the tissue character of pericardium with MRI. Hemodynamic catheterization is still the gold standard diagnostic test and may be necessary when noninvasive studies remain unclear. Increased RA and RV-end diastolic pressure with near equalization of right and left heart diastolic filling pressures, deep y descent in RA pressure tracing and inspiratory fall in PCWP greater than LV diastolic pressure are the classical findings. Careful integration of historical features as well as physical examination, laboratory and cardiac test results must be required for an accurate diagnosis. Even cardiac catheterization can be tricky that the features mentioned above may also be present in RC. And patients undergoing aggressive diuresis have generally lower filling pressures, a fluid challenge of 500 mL saline may be required to disclose the physiology.

Making diagnosis may be difficult, as it mimics other disorders. Right ventricular filling was impaired throughout diastole in cardiac tamponade due to compression of high-pressure pericardial fluid around heart, however the earliest phase of diastolic filling did not impair in CP. Additionally, Kussmaul's sign, pericardial calcification and abnormal S_3 were absent in tamponade. In RC, systolic functions of both ventricles are impaired in contrast to normal left ventricular systolic function in CP. This can be identified with a normal PCWP of CP in catheterization. On the side, constriction causes more equalization of diastolic pressures with a

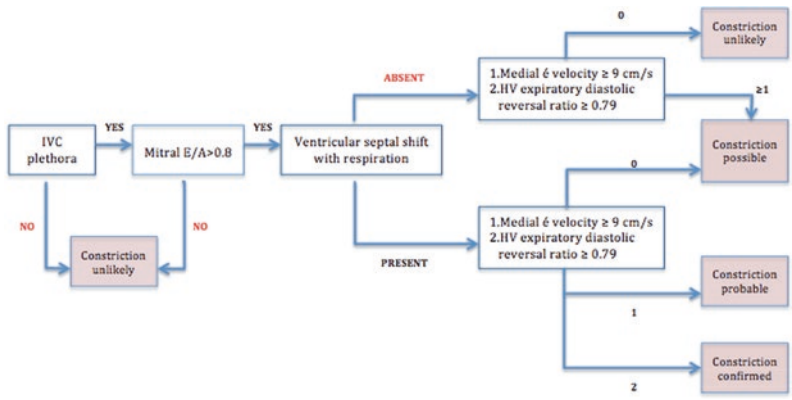

Fig. 1 The Mayo clinic criteria for diagnosis of CP

calcified shell around ventricles that is showed by identical LA/PCWP and RA pressures. In restriction, there is difference in LA and RA pressures (>6 mmHg). Hemodynamic change in PCWP/LVEDP with exercise rises markedly in RC against minimal rise in CP.

To sum up, all patients presenting elevated jugular venous pressure, edema, hepatic congestion or pleural effusion should be evaluated for CP, especially had a history of cardiac surgery or chest irradiation.

Medical Treatment

Given the fact that early surgical treatment is associated with better outcomes, patients with chronic constriction should not be delayed for intervention [16]. Additionally, symptomatic recurrences refractory to anti-inflammatory therapy should also be treated surgically. But initially, exercise restriction with medical treatment consisted of NSAIDs, colchicine and corticosteroids can be an option for relapsing pericarditis. Patients with severe infection, reduced life expectancy due to fatal systemic diseases and end-stage pathophysiology, such as cirrhosis, cachexia or low cardiac index <1.2 L/m^2/min, might be the unclear contraindications due to increased procedural risk.

Subacute CP generally responds to steroids if treated before the fibrotic process settled. Diuretics are the main weapon to optimize clinical volume and to control congestion, however close monitoring is required in case of reduced cardiac output by decreased preload. Patients expressing mild symptoms can be treated medically up to three months with close monitoring for symptomatic progression. Anti-inflammatory medications may cause spontaneous resolution in acute or transient disease. Transient CP mostly occurs after cardiac surgery, followed by trauma or infection and idiopathic. Report from Mayo Clinic concluded a spontaneous resolve in 17% of CP cases after 8.3 weeks of medical therapy [20]. NSAIDS and steroids are mostly effective treatments. Colchicine is understood to be effective in derogating relapsing [21, 22]. Cardiac MRI may help for the decision of pursuing the medical modality [23]. Any other medications can be used towards the causative disease, e.g., antituberculosis therapy. Beta- or calcium canal blockers should be avoided; because sinus tachycardia is the compensatory respond for maintaining cardiac output. CP is progressive and eventually chronic in most of the cases leading to a definite treatment of surgical pericardiectomy.

Surgical Approach

Pericardiectomy has been a curative therapy since 1913s [24]. A consensus has not been reached regarding the surgical technique of CP including the incision choice or the extension of pericardiectomy. However surgery is the only effective treatment for symptomatic CP patients. Preoperative planning is similar to other cardiac operations. Short acting muscle relaxants were preferred during dissection of phrenic nerve to avoid injury. In advanced heart failure patients, volume status can be optimized with diuretic therapy. Intraoperative TEE must be used to assess cardiac recovery as well as obtain any residual atrioventricular valve failure after releasing the inflammatory adhesions [25].

Especially TI may worsen due to further annular dilatation by getting loose of constriction effect around atrioventricular junction following pericardiectomy, and it is already known that persistency of the valve has reduced survival. Preoperative TI more than moderate was associated with 21% of the patients [26]. Ongoing significant TI, which progresses with pericardiectomy, will affect long-term outcome and is a risk factor for mortality by giving cause for right ventricular failure. Hence concomitant valve annuloplasty should be performed in patients with $\geq$3 valvular regurgitation [2, 11, 16]. Moreover similar genuine about the mitral valve has been debated with enhancing failure after pericardiectomy [27].

Due to the fact that fibrosis and severe adhesion occur between pericardial layers, excision of the pericardium ventrally to the phrenic nerve

may cause nerve injury. To evade that, nerve stimulation might be handy for phrenic nerve identification.

Cardiopulmonary Bypass

Previous studies mostly concluded that routine CPB utilization for total pericardiectomy is unnecessary. However it should be conform in some chosen cases [28]: 1. Presence of severe calcific 'cocoon' pericardium bearing all cardiac chambers, 2. Patients with previous cardiac operations or needing pericardiectomy after chest irradiation, 3. Patients with concomittant cardiac problems requiring correction, 4. Unintentional complication to cardiac chambers.

In our institution, we prefer to perform the pericardiectomy on CPB so that we can excise as much as possible including the posterior and inferior part of the ventricle to the left pulmonary veins. Hemodynamic support with CPB will help to manipulate the heart during explosion; and, intravascular volume can be adjusted easily after pericardiectomy by CPB for adequate cardiac output. Cardiac decompression helps the removal of heavily calcified pericardium, particularly when penetration is deeper into myocardium. Mostly, aorto/two-stage single venous cannulation, if there is no cardiac pathology, without cross clamping is sufficient. Bicaval cannulation should be considered prior to surgery in the presence of TI more than moderate. A simple de Vega annuloplasty can be sufficient in most patients, however ring annuloplasty would be the right choice when there is annular dilatation or pulmonary artery systolic pressure $\geq$50 [29].

This is technically a demanding surgery that it is possible to have myocardial, coronary artery or phrenic nerve injury in which early CPB support is beneficial. Mayo Clinic had declared the use of CPB in 60% of the patients since 1990 with more than 800 patients; they also stated that aortic cross-clamp was utilized in one-third of patients [30]. However, Chowdhury and colleagues clearly stated CPB is not necessary with 2% of 338 patients undergoing radical pericardiectomy [31].

Generally, CPB is reserved on standby in case of the need when there is serious bleeding or difficult dissections. This would help to prevent poor distal perfusion due to cardiac lifting and positioning. Opposed to these advantages, CPB use can be hazardous with excess bleeding and was avoided when possible. Being aware that CPB unloads the heart, it may become more difficult to excise the pericardium. Vacuum positioning devices are easily used for cardiac manipulation during off-pump surgery.

Incision

The extent of pericardial resection as well as surgical incision has evolved during the last two decade. Pericardiectomy mostly performed through either median sternotomy or left anterolateral thoracotomy. Median sternotomy is usually the preferred option because it offers a wide vision to access great vessels, and furthermore, helps to control the bleeding and enables to use CPB in urgency or for performing other procedures [26, 27]. Midline sternotomy should also be a preferred access in patients having poor pulmonary functions.

In the presence of concomitant pyothorax due to purulan or effusive pericarditis, left anterolateral thoracotomy becomes the preferable approach to avoid sternal infections; and probably, it would be easier to peel off the pericard due to poorly formed adhesions with effusion. But it is hard to access to the right heart, as well as to perform concomittant cardiac repairs; so an additional right thoracotomy, alias bilateral thoracotomy, or femoral cannulation when CPB is needed might be a useful trick. Even though bilateral thoracotomy is risky for patients with respiratory problems, it can be useful in redo operation. Interestingly, Lanchman and associates showed the access ratio to left ventricle and total pericardium, in which left anterolateral thoracotomy is superior to midline sternotomy (26% and 58%, versus 37% and 63%, respectively) [32]. However this study was valuated on idiopathic CP, and did without including the excision of diaphragmatic pericardium.

Nevertheless centers mostly utilize this approach for cosmetic considerations. We, on the other hand, prefer midline sternotomy for nearly all patients for ensuring adequate extent of peeling and cannulation when needed. In some studies, incisions except total pericardiectomy are also sufficient because of less need for systemic heparinization and CPB, easier access to cardiac chambers. As a consequence of these advantages, they concluded a satisfactory operative mortality with NYHA improvement and long-term survival [11, 33, 34].

Extend of Pericardiectomy

Even though partial pericardiectomy has been recommended in some circumstances [16, 35], complete pericardiectomy remains the potential cure in most patients [30]. The terms 'partial/complete/radical pericardiectomy' or 'subtotal/total pericardiectomy' have been displacing over decades. Complete/Total pericardiectomy was depicted as removal of whole pericardium including the great vessels and the diaphragmatic surface; retroperitoneal segment, posterior pericardium between pulmonary veins in the oblique sinus, should not necessarily be peeled off [31]. So, any excision less than described previously would be considered as partial pericardiectomy [4, 31]. Anterior pericardiectomy has been described as pericardial removal between left and right phrenic nerves, which is believed to be limited. But the basic idea of this surgery is that it restrains the injury to and the technical complexity of exposing the posterior and inferior parts which covers the considerable part of the left and right ventricle of the heart and, also improves the constrictive hemodynamics in most patients [33, 36].

In addition to previous descriptions, radical pericardiectomy is represented by the removal of the anterior pericardium, as well as posterior of left phrenic nerve and diaphragmatic pericardium [36]. Thus, Nozohoor and colleagues showed increased 10-year survival rates and NYHA functional improvement with radical compared to subtotal pericardiectomy [37]. Many surgeons perform radical pericardiectomy on behalf of total pericardiectomy, and this technique becomes the standard approach in most large series [26, 31, 33, 35]. In a retrospective study of Chowdhury et al. radical pericardiectomy resulted with lower perioperative and late mortality, and showed better long-term hemodynamic improvements rather than anterior pericardiectomy, even if the morbidity was higher in total group [31].

If the purpose of resection is for treatment of recurrent pericarditis, the only solution will be the excision of as much pericardium as possible. Cho and colleagues reported that failure of diaphragmatic pericardium, as well as inferior aspect of both ventricles causes residual constriction and recurrency [21, 38]. Pericardiectomy lesser than complete only destroys the circumferential constriction effect; base and left lateral portion of the heart are still encased leading to ventricular dysfunction, and consequently recurrence.

The Operation

Patients were fully monitorized throughout the surgery to notice the hemodynamic changes. Preparation for anesthesia is same as routine practice in other cardiac surgeries. Minimal paralysis would be helpful during dissection of phrenic nerves. Intraoperative TEE and pulmonary artery catheter are essentials to reclaim the changes in valvuler functions and cardiac sizes [26, 27, 31]. It is crucial to assess the competence of the tricuspid valve following pericardiectomy. CPB circuit is ready to use in all cases. Pericardiectomy can be performed through median sternotomy, left anterolateral or bilateral thoracotomy, and the incision can be decided by surgeon's preference depending on additional interventions and the patient's history. Nevertheless, median sternotomy has been the favored approach in remarkable majority of centers.

Slightly right positioning of the patient with groins being ready for urgent exposure in case of CPB need, is favorable for left anterolateral

thoracotomy. Fourth or fifth (patients with left ventricular enlargement) intercostal space following submammary incision provides excellent access to left side of the heart, as well as right atrium. Reaching to posterior pericardium is an advantage of this approach when CPB is not used after midline sternotomy. Cannulations of axillary or femoral artery with femoral vein are performed when CPB is necessary. The patient is prepared in standard manner for traditional pericardiectomy with median sternotomy.

It can be extremely challenging to identify a proper plane between pericardium and epicardium in the presence of heavy calcification invaded to myocardium. The coronary arteries are clearly visualized when the dissection plane is accurate. Normally there won't be any bleeding if you cut the plane between parietal and visceral layers of pericardium hence this area is avascular. However the maneuver may result with injury if there is a heavy calcification between epicardium and the parietal pericardium. Rongeure can be an option for these adhesive areas when total decalcification might be detrimental. To avoid injury to coronary arteries in the presence of notably myocardium invasion, the constricting layers of epicardium can be incised as a waffle-like pattern, which is called The Waffle Procedure [39]. Serial transverse and longitudinal incisions resembling square blocks are the base of this procedure (Fig. 2). The relief of this intense epicardial constriction is performed without CPB, and an apical suction device is mostly sufficient. Furthermore, the incisions need to be deep enough into the myocardium and that can cause bleeding problem. Matsuura and colleagues use ultrasonic scalpel for making epicardial incisions without CPB by the help of an apical suction device [40]. First, superficial incisions might be done with a 15

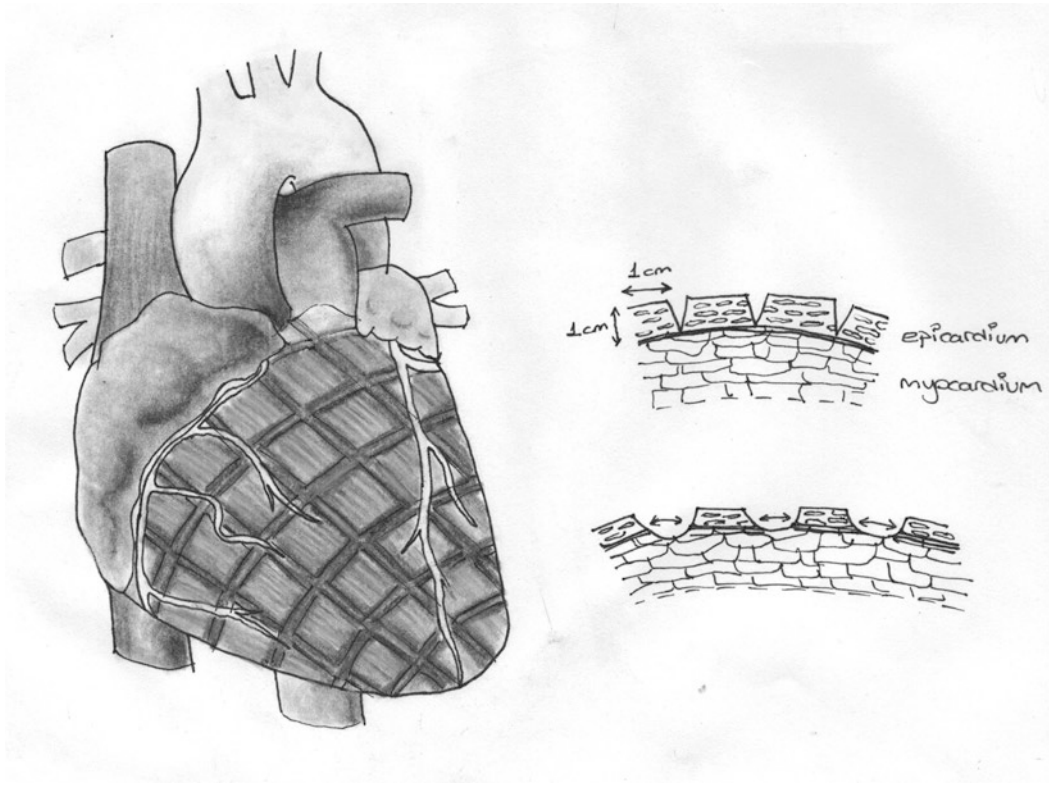

Fig. 2 In Waffle procedure, longitudinal and transverse incisions are utilized to underlying constricting epicardium after the resection of pericardium by forming 1-cm^2 islands of scar tissue (waffle-like pattern)

blade; afterwards, scalpel is used to form deeper cleft longitudinally and transversely.

The pericardium is divided in midline or wherever that has free line for incision is present after median sternotomy. Initially, both pleural cavities are opened to identify the phrenic nerves. The anterior line of pericardiectomy starts 1–1.5 cm anterior to the nerve; and, can be done from pleural side. You have to pay attention that the nerve runs anteriorly in the upper part of mediastinum, so the incision should be performed carefully. Dissection should be done with scissor and electrocautery or harmonic scalpel, and must include both serous and fibrous layer of visceral pericardium. Otherwise, we won't be able to visualize the coronary arteries. On condition that CPB was already planned, dissection should be started over the aorta and then RA. And if the adherence on RA is firm, the superior vena cava can easily be exposed from inside or outside the pericardium for venous cannulation. Sometimes adhesions are loose enough to disarticulate from the heart by sponge forceps. The conventional resection should begin with the LV before the RV. Right ventricular failure and pulmonary edema, consequent to massive preload to the left ventricule, can be resulted if the RV released before LV. However, it is mostly formidable to decorticate LV first without CPB; so the dissection begins with mid-anterior part including the right side first, and then proceeds laterally to left side. Following the decortication of both ventricle, atrium and cava were dissected respectively (Fig. 3). The resection lateral to pulmonary artery can cause injury to phrenic nerve; namely, it may be inessential to treat adhesions in that area. One of the important steps of this procedure is decompression of right cavities regardless of the size of resection, because most patients apply with right-sided complaints, which is hemodynamically significant. So, median sternotomy allows better vision of pericardium overlying the right atrium

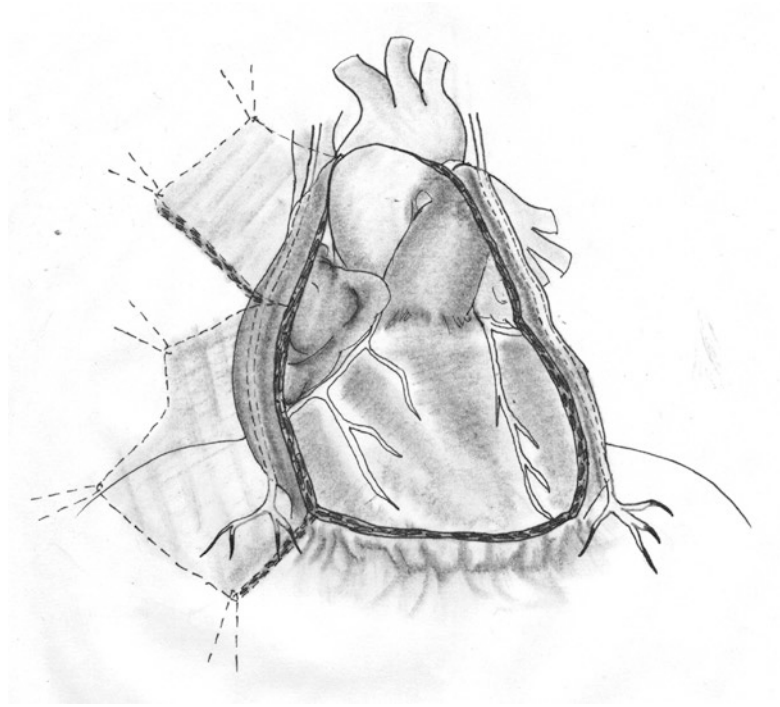

Fig. 3 The anterior mediastinal dissection was performed initially with entering both pleural spaces to view the phrenic nerves. The lateral extensions are limited to 1 cm anterior to the right and left phrenic nerves. The left anterior descending artery is well visualized following the removal of anterior pericardium

and venae cava as a radical solution. Chowdhury et al. described a modified left anterolateral thoracotomy (UKC's modification) to obtain a new dissection plane for better exposure of right atrium and ventricle, as well as posterolateral surface of left ventricle and atrium [28].

Excision is then continued with the diaphragmatic pericardium. The diaphragm is a muscular structure, where the resection from inferior surfaces of membranous pericardium overlapping ventricles won't be demanding [38]. Any defects in diaphragm after dissection can be repaired directly or with a patch. Then the dissection was continued to posterolateral wall, lateral to left phrenic nerve down to left pulmonary veins and the inferior part of both ventricles (Fig. 4). An apical suction device can be used for this manipulation. At the end, the atrial inflows of superior-inferior vena cava and right-left pulmonary veins and the ventricular outflows of pulmonary artery and ascending aorta are purified. Routine pericardial biopsy should be sent for identification.

Postoperative Management

The course of the patients, which is very variable, depends on the surgical accomplishment. Following the surgery upon the degree of organ

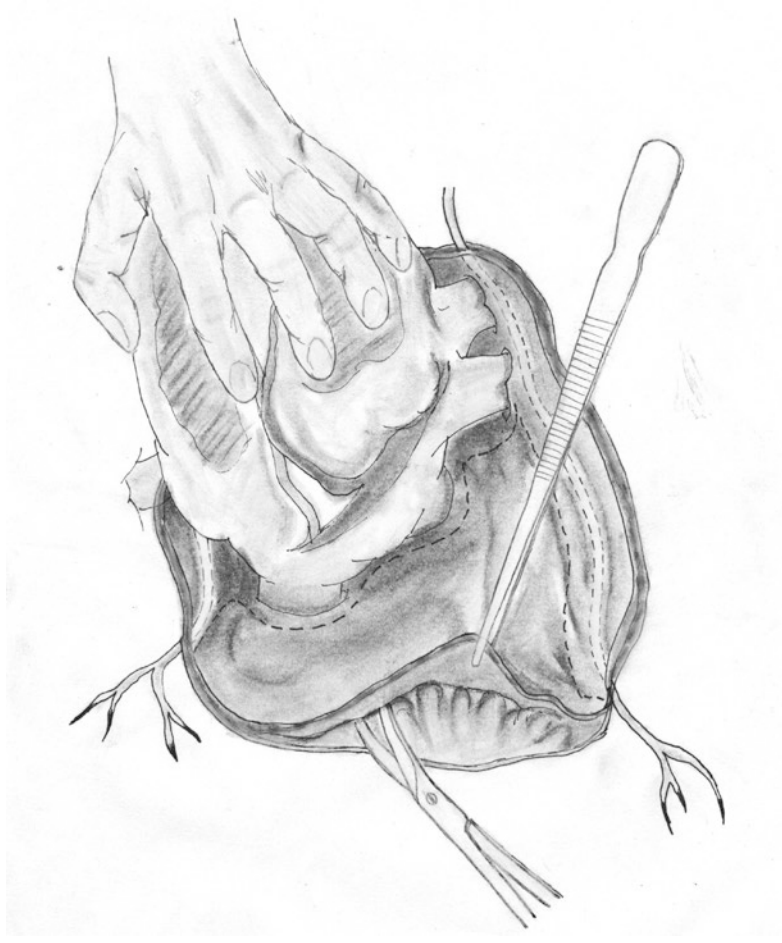

Fig. 4 Additional dissection starting with the diaphragmatic pericardium from inferior left and right ventricular and posterolateral left ventricular walls is done. More attention should be taken not to harm the left phrenic nerve due to its proximity. Then it is followed by removal of the posterior pericardium

dysfunction, changes in filling may cause failure. Hemodynamic monitoring must be maintained in the intensive care unit. The major complication is LCOS postoperatively. With the disappearance of external support to the heart, cardiac dilatation is revealed and substantial myocardial atrophy leads to failure. Particularly, patients with radiation induced pericardial constriction may have underlying ventricular dysfunction that comes off after pericardiectomy and these patients still have ongoing clinical signs (e.g., venous congestion) [25, 41]. Injury to epicardial coronary arteries might be another reason for this situation [42]. In such case, supportive treatment should be established immediately. Postpericardiectomy LCOS occurs up to 30% of the patients [3, 4]. The pathophysiology can be deflectable to incomplete decortication, abnormal diastolic filling, worsening tricuspid valvular disease, remodeling of the ventricle [4, 35]. If the cardiac output cannot be sustained by volume maintenance or medical treatment, mechanical circulatory support (intraaortic balloon pump, extracorporeal membrane oxygenation, etc.) should be the next strategy to support the failing heart. Dobutamine had already been given due to the benefit of inodilatation as the choice of a potent inotropic agent. Chowdhury et al. searched the literature for balloon counterpulsation with failing circulation postpericardiectomy. IABP helps ventricular interdependence indirectly via pulmonary ventricle and left ventricular recovery by reducing LVED and LA pressures. However, they reported three survivals out of seven [43].

Outcomes

Patients mostly experience hemodynamic improvement after pericardiectomy. Nevertheless, etiology and severity of the disease and the comorbid features influence the degree of recovery after surgery, particularly those with advanced NYHA functional class, low LVEF and comorbidities [31, 34, 42].

In spite of the increased surgical experience and advanced techniques, there is still wide range of operative mortality. Earlier studies had reported 6 to 11% and in the current era, these rates are getting better related to improved surgical experience and techniques and postoperative care [3, 4, 31, 35]. It has been reported that idiopathic etiology has survival rates of >80% at 5 years which is the best outcome among all [3, 4]. Unlikely, patients with chest irradiation have opposite with survival rates up to 30% at 5–10 years [4, 35]. However most of the patients surviving long-term gain symptomatic benefit more than 80% with pericardiectomy except in patients with older age, impaired renal and hepatic functions and advanced functional class of NYHA [29, 30, 36].

Even with these decent rates in mortality, the survival has not improved as predicted. Functional class, etiology, age, the presence of right-heart failure are determined risk factors for survival [26, 35]. The durability of disease and the severity of RHF are the most important variables documented in many studies with a conclusion of increased risk of death [3, 5, 44]. Based on those predictors mentioned above, early diagnosis and treatment modality will help to improve survival. However, it is unavoidable that the etiology has a significant impact on long-term survival. Patients with previous radiation exposition have low late survival apparently [35, 41]. The radiation therapy itself causes restrictive cardiomyopathy and myocardial fibrosis, which makes the dissection more complicated. In these patients, not only the survival is reduced, but also they will typically experience recrudescent symptoms of functional class III-IV. On the other hand, the clinical improvement of patients and survival are satisfactory for remaining etiologies. Some of the major studies published 5-year survival of 78% from Mayo clinic, 79.8% from John Hopkins hospital, 87.5% from Montreal Heart institute [4, 5, 16].

Recurring symptoms depend on underlying myocardial disease, but broadly speaking it is secondary to residual constrictive pericarditis. Remanent diastolic dysfunction may last in substantial amount of patients; even Hemmati et al. reported 43% of patients who had abnormal diastolic dysfunction 3 months after surgery [45].

However this situation should not be directly associated with an impairment in functional status because most analysis showed significant improvement with more than 80% in NYHA functional class III-IV postoperatively [11, 45].

Conclusion

Even though the operative mortality of CP still remains high, the long-term outcomes are satisfactory. Pre- and intraoperative factors, related to the patients' clinical features, can adversely possess the short-term outcome. The main goal in pericardiectomy is to improve cardiac functions; and accordingly, primary etiology should be identified and eradicated. Surgery definitely cultivates hemodynamic abnormalities causing impressive recovery clinically. Clinical outcomes are connected with resolving the constrictive physiology by excessive restrictive pericardial removal, thus patients were ended up with reduction in RA pressures. Total/Radical excision allows the cardiac chambers to re-expand resulting the end-diastolic pressures consequently RA pressures decrease. This hemodynamic adaptation is indeed an important prognostic indicator, and causes remarkable clinic improvement. The favored technique has become radical pericardiectomy almost in all clinics, however the effectiveness of alternative approaches (thoracoscopic or robot-assisted partial/total pericardiectomy, etc.) has not yet gained popularity. Nevertheless, these methods may be applicable for selected patients.

Eventually the disease can lead to heart failure and worsen the patient's clinic over time, and poor preoperative functional class with older age has negative influence in outcome. So, early intervention must be taken into account as soon as possible.

In the future, thoracoscopy and robotic endoscopic approach for partial or anterior pericardiectomy will become increasingly popular to minimize the mortality, as well as morbidity associated with median sternotomy [46, 47]. Having an extensive heavily pericardial calcification, it is not recommended to use these methods due to lack of visualization and inadequate instrument mobility. Maciolek and colleagues had preferred totally endoscopic robotic-assisted off-pump technique in 20 patients due to shorter hospital stay, less postoperative pain and importantly, lower early and midterm mortality rate [47]. They specifically pointed out that surgical approach from left pleural space offers excellent visualization of posterior pericardium, and they believed that it helps to remove adequate pericardium.

Self-study

1. Which one is the most common cause of constrictive pericarditis in developing countries?
   a. Viral
   b. **Tuberculosis**
   c. Myocardial infarction
   d. Bacterial.

2. Which is the most injured nerve during pericardiectomy?
   a. Vagus nerve
   b. Recurrent laryngeal nerve
   c. Cardiac plexus
   d. **Phrenic nerve**.

3. Which of the following is not the echocardiographic signs of constrictive pericarditis?
   a. Septal bounce
   b. **Decreased medial mitral é velocity (>9 cm/s)**
   c. Respiratory variations of transmitral and tricuspid flows
   d. Inferior vena cana plethora.

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Malignant Pericardial Effusions

Claudiu E. Nistor, Adrian Ciuche, Ecaterina Bontaș, and Teodor Horvat

Key Points

- In the case of malignant pericardial effusions, available therapeutic methods are pericardiocentesis, subxiphoidal pericardiotomy, pleural pericardial window, peritoneal-pericardial window, and pericardiectomy
- Percutaneous balloon pericardiotomy is also used as an alternative to pericardiocentesis and pericardoscopy as a diagnostic method
- The immediate prognosis of malignant pericardial effusions is influenced by the risk of postoperative low cardiac output
- The late prognosis is closely related to the type of malignant tumor, which caused the malignant pericardial effusion.

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Definitions

Pericardium is the protective coating of heart and of large vessels. It is made up of two serum sheets: a thin visceral membrane (visceral pericardium) and a fibrous parietal membrane (parietal pericardium). The pericardial space bounded between both membranes normally contains about 50 ml of pericardial fluid. Fibrous pericardium contains collagen and elastic fibers which give elasticity to pericardial layers. This allows for large amounts of liquid accumulation in the pericardial space without significant changes in the pericardial fluid pressure over the progressive distension of fibrous pericardium. When the pericardial fluid volume exceeds stretch of pericardial fibers ("beyond the membrane stretch limit"), the cardiac tamponade is installed. Also, rapid accumulation of pericardial fluid may lead to sudden increase in pericardial pressure with the occurrence of cardiac tamponade.

Occurrence of pericardial effusion associated with cancers is considered to be a complication of the progress of these neoplastic processes. Cancers can directly affect the pericardium (pericardial tumors, cardiac tumors, direct invasion of nearby cancer, or pericardial metastasis of distant tumors) or indirectly (as side effects of radiotherapy, chemotherapy and secondary immunodepression of opportunistic infections such as viral or bacterial

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pericarditis). In the first case, when we identify the presence of malignant cells in pericardial fluid or in biopsy of harvested pericardial tissue fragments, it is true malignant pericarditis. In the absence of malignant cells in the pericardial fluid, pleural effusions may be considered paraneoplastic (paraneoplastic pericarditis) [1–5].

Etiopathology—Short Uptodate

Most malignant pericarditis develop as a complication of the evolution of lung cancer. Other cancers that can often associate pericardial effusions are: lymphoma, leukemia, malignant melanoma, breast, ovarian, prostate, colon, gastric, renal, and bladder cancers. Primary pericardial or cardiac cancers (mesothelioma, fibrosarcoma, angiosarcoma) are rare and their association with pericardial effusions is also rare [1, 4].

Serous pericardium may be invaded indirectly by haematogenic or lymphatic pathways, or may be invaded directly by the malignant tumor.

Metastasis may develop in the fibrous and/or visceral pericardium, but also in the myocardium and endocardium. Descending order of frequency is the pericardial metastases, myocardial metastases, and endocardial metastases. All three topographic areas of heart may be affected simultaneously [6].

Pathogenesis of metastasis is generally the one mentioned above, however there are variations depending on the type of malignant tumor.

An important role in the appearance of malignant pericarditis is the lymphatic circulation of pericardium and heart, consisting of three lymphatic plexuses (pericardial, subepicardial and subendocardial), which drain pericardium and heart lymph into mediastinal lymphatic nodes. Lymphatic pericardial metastasis is done retrograde, so that metastases from the mediastinal lymph nodes end in the subepicardial lymphatic network that is best developed. This explains the greater frequency of epicardial metastasis and lower frequency of the metastases in the fibrous pericardium, and the common situation in which only malignant cells are present in pericardial fluid without malignant cells in the fibrous pericardium accessible to surgical pericardial biopsy [3, 7].

In 1/3 of cases, direct invasion by tumor in the pericardial sac is not followed by the appearance of effusion.

Physiopathology—Short Uptodate

Perturbation of pericardial fluid turnover, which can daily reach a volume of 20 l (secretion/resorbtion by venous and lymphatic vessels) can cause fluid accumulation in the pericardial cavity.

Depending on the accumulation rate, function of the heart may be affected brutally or progressively [4].

In rapid accumulations, cardiac tamponade can precipitate to 250 ml of pericardial effusions. While in slow accumulations, the heart function can be maintained at a volume of 3000 ml of pericardial fluid.

Presence of pericardial fluid may affect filling of heart as well as the heart pump function. Increased intrapericardial pressure has a particular effect on the right heart due to the thin walls of atrium and right ventricle.

Normally the right atrial pressure is higher than the intrapericardial one. As fluid accumulates in pericardial space, the pressures tend to equalize so that in case of cardiac tamponade there is a decrease of the right atrium filling and right heart failureheart failure with altering of left ventricular pump. Alteration of heart function leads to the occurrence of left ventricular failure. Thus, cardiac output decreases with sympathetic adrenergic stimulation with increased circulating catecholamine concentrations, which is manifested by tachycardia, increased ejection fraction and peripheral vasoconstriction, phenomena that try to compensate for low cardiac output. Untreated on time, cardiac tamponade is worsening with overwhelmed compensatory phenomena and blood pressure collapses when the danger of death is imminent [8–10].

Surgical Approaches

In the course of time, various therapeutic procedures have been applied with the aiming (1) to evacuate pericardial effusion for avoiding cardiac tamponade, together with (2) biopsy and pericardial fluid analysis to specify the etiopathological diagnosis, and (3) to eliminate pericardial space for prevention of pericardial effusion recurrence [4].

In contrast to pericardial effusions of other aetiologies, malignant pericardial effusions present an increased risk of rapid fluid accumulation in pericardial sac with the onset of cardiac tamponade phenomena. Diagnosis on time of cardiac tamponade is of vital importance for the patient because the haemodynamic phenomena accompanying this pathological entity can lead to patient death in the absence of pericardial fluid drainage.

Currently, in the case of malignant pericardial effusions, available therapeutic methods are (1) pericardiocentesis, (2) subxiphoidal pericardiotomy, (3) pleural-pericardial window, (4) peritoneal-pericardial window, and (5) pericardiectomy. Percutaneous balloon pericardiotomy is also used as an alternative to pericardiocentesis and pericardoscopy as a diagnostic method [11].

Pericardiocentesis (Percutaneous Pericardial Drainage)

Pericardiocentesis is the percutaneous technique of pericardial drainage that is performed under local anesthesia (Fig. 1) [12]. It is indicated in emergency situations when malignant pericardial effusion is complicated by cardiac tamponade phenomena. In these situations, open surgical procedures have the main disadvantage of general anesthesia with the risk of sudden severe hypotension [13].

Over the past decades, pericardiocentesis was performed as a "blind procedure" and almost exclusively in the subxiphoid area.

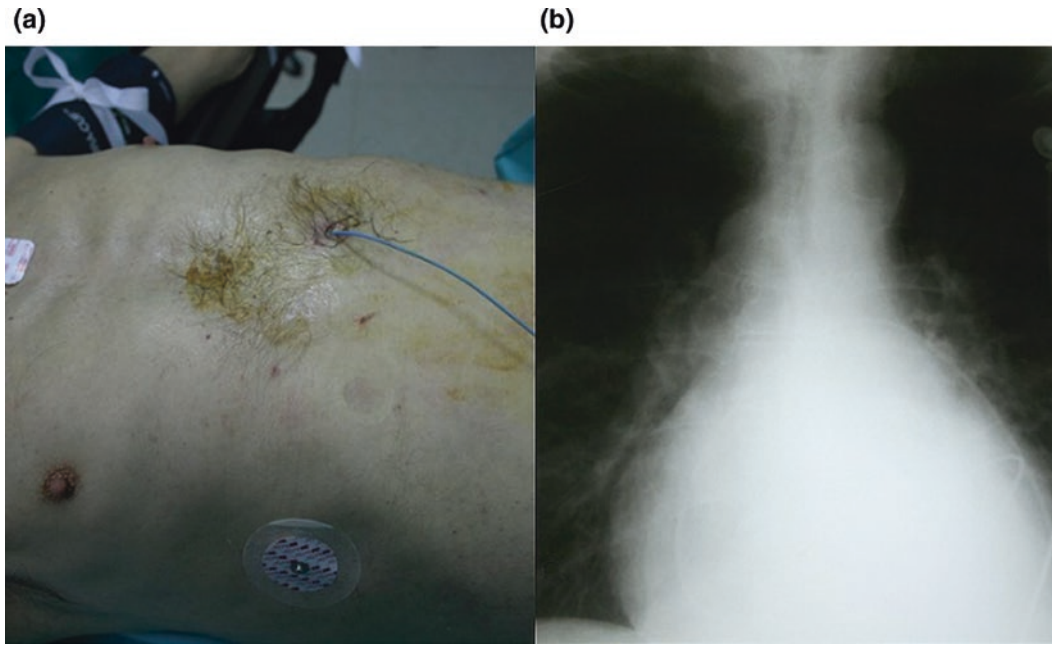

Fig. 1 **a** Pericardiocentisis with catheter insertion; **b** chest X-ray showing pericardial catheter winded to the pericardium [12]

Current guidelines have established that pericardiocentesis must be performed under echocardiographic guidance, only to reduce the risk of heart damage. Echocardiography identifies the best place for pericardial puncture (at the level of closest area to the large amount of effusion), this area most frequently was found to be subxiphoid. In some cases, the best place for pericardiocentesis may be located at the left parasternal or even left lateral thoracic region [13].

The European Society of Cardiology (2014) proposed for patients requiring urgent percutaneous or surgical drainage of pericardial effusion a calculation system based on the cumulative score of three stages of diagnosis (etiological, clinical and imaging) (score ≥6) (immediately after the contraindications are ruled out) or who can be postponed 12–48 hours to perform surgical drainage under general anesthesia (score <6) (Table 1) [13]:

Shortly, three main approaches are used in pericardiocentesis: (1) the subxiphoid (subcostal) approach, (2) the parasternal approach, and (3) latero-thoracic (apical) approach, under the echocardiography—guided approach (with or without continuous ultrasound visualization).

Pericardiocentesis should be avoided in certain situations that are considered to be contraindications to this invasive maneuver: (1) anticoagulation therapy with INR >1.5, (2) thrombocytopenia <50000/mm^3, (3) small effusion or posterior effusion or loculated pericardial effusions. In the presence of severe coagulation disorders, pericardiocentesis should be performed after platelet or plasma administration (pericardiocentesis has to be postponed

Table 1 A proposed three-step scoring system of evidence of cardiac tamponade for triage of patients requiring urgent pericardiocentesis (score ≥6) or surgical pericardial drainage (score <6). (PE, pericardial effusion; SBP, systolic blood pressure; HR, heart rate; IVC, inferior caval vein). Modified from [13]

Step 1 (score the aethiology)	Malignant disease	(2)
	Mediastinal radiotherapy	(1)
Step 2 (score the clinical presentation)	Dyspnea/Tachypnea	(1)
	Orthopnea (no rales on lung auscultation)	(3)
	Hypotension (SBP <95 mmHg)	(0.5)
	Progressive sinus tachycardia	(1)
	Oliguria	(1)
	Pulsus paradoxus >10 mm Hg	(2)
	Pericardial chest pain	(0.5)
	Pericardial friction rub	(0.5)
	Rapid worsening of symptoms	(2)
	Slow evolution of the disease	(−1)
Step 3 (score the imaging)	Cardiomegaly on chest X-ray	(1)
	Electrical alternans on ECG	(0.5)
	Microvoltage in ECG	(1)
	Circumferential PE (>2 cm in diastole)	(3)
	Moderate PE (1–2 cm in diastole)	(1)
	Small PE (<1 cm in diastole)	(−1)
	Right atrial collapse >1/3 of cardiac cycle	(1)
	IVC >2.5 cm, <50% inspiratory collapse	(1.5)
	Right ventricular collapse	(1.5)
	Left atrial collapse	(2)
	Mitral/tricuspid respiratory flow variations	(1)
	Swinging heart	(1)

until sufficient blood for transfusion, platelets, or coagulation factors are provided) [9].

The guide can be made by anatomical markings (the needle will have a skewed direction ascending to the tip of left scapula) or by the ultrasound control or under fluoroscopic control. The heart rate will be monitored.

Pericardiocentesis is performed with a special catheter (or pigtail catheter) or, if not available, a standard central venous catheter 7F can be used (Fig. 1) [12].

Once the pericardial space has been penetrated, liquid is collected for biochemical and cytological examinations. A small catheter may be inserted into the needle, which will be left in situ for a few days [14, 15]. Through the percutaneous pericardiostomy catheter, sclerotherapy may be performed [6, 16].

Pericardiocentesis is not without risks, cardiac wall or coronary artery can be damaged, or major arrhythmia may occur. It is the method with the highest procedural induced mortality. Thus sonographic guided pericardiocentesis recorded a rate of 1.3–1.6% major complications [15]. And the puncture of pericardium under fluoroscopic control had a higher rate of accidents and complications: heart rate perforation—0.9%, arterial bleeding—1.1%, pneumothorax 0.6%, severe arrhythmias 0.6%, major vagal reactions 0.3% and infections 0.3% [15, 17, 18].

Echocardiographic control of correct placement of the drainage catheter in the pericardial space can be done by injecting a small amount of air microbubbles into the catheter by agitation (agitated saline solution). In the case of cardiac chamber perforation during pericardiocentesis in a patient with cardiac tamponade, the perforation catheter should not be removed from the cardiac wall until pericardial fluid is drained through another pericardial catheter. The perforation catheter is extracted only after successful placement of a new catheter in the pericardial space, with autotransfusion (autologous blood transfusion). In some cases, depending on the size and location of the laceration in the cardiac wall, this technique can postpone cardiac surgery. If the patient remains unstable hemodynamically, the repair of heart damage should not be delayed [13].

Pericardiocentesis drainage of more than 1 L of pericardial fluid should be avoided due to the risk of installing of a cardiac low output syndrome. This syndrome may manifest by acute pulmonary edema, circulatory collapse, acute right or left ventricular dysfunction. Evacuation of the pericardial fluid should be done slowly and intermittently (every 4–6 hours) with the maintenance of the pericardial catheter as long as the pericardial drainage exceeds 20–30 ml/24 hours [13]. Prolonged pericardial drainage is recommended especially for neoplastic pericardial effusions (at increased risk of relapse) to prevent recurrence, caused by intrapericardial fibrous adhesions.

Pericardiocentesis is followed by a relapse in a significant number of cases, however the immediate success rate is over 95% [9].

To prevent relapse, it is advisable to introduce sclerosing, or cytostatic, or radioisotope (P^{32}) substances through the catheter [6, 16, 19].

Reynen and colleagues described the sclerosing, or cytostatic, or radioisotope (P^{32}) substances that can be used, including the doses, the frequency of injections, the side effects as next [3]:

- Tetracycline derivatives—15 mg/kg body weight (500–1000 mg) in 20–50 ml physiological saline solution, with 1–5 number of applications, and possible side effects: fever>38.5°, pain, cardiac arrhythmias;
- Bleomycin—dose 5–60 mg in 10–20 ml physiological saline, with 1–2 number of applications, and possible side effects: fever;
- Cisplatin—15 mg dose in 20 ml physiological saline or 30 mg/m^2 in 100 ml physiological saline, number of applications 1–5 (first dose of 15 mg), 1 application for 2nd dose of 30 mg), side effects: pain, nausea, myocardial ischaemia, atrial arrhythmias;
- Thiotepa—15 mg dose in 20 ml physiological saline or 30 mg in 20 ml physiological saline, number of applications 3 (first dose of 15 mg), 1 application for second dose of 30 mg), side effects: leucopenia, thrombocytopenia;
- Mitomycin C—8 mg dose in 10 ml physiological saline, number of applications 1–3, side effects: constrictive pericarditis;

- Mitoxantrone—dose 10–20 mg, number of applications 1–3, no side effects;
- 5-Fluorouracil—250 mg dose in 20 ml physiological saline, number of applications 1, side effects: neutropenia;

Prior to instillation of tetracycline products (vibramycin), intrapericardic will be given xylin at a dose of 100 mg for pain prophylaxis.

The success rate of 75% recommends pericardiocentesis + pericardial sclerotherapy as an effective method of treating malignant pericardial effusions [3].

Percutaneous Balloon Pericardiotomy

Method involves creation of a pericardial window by laceration of fibrous pericardium using a single balloon or two balloons. It is performed with ultrasound or fluoroscopic control by percutaneous introduction at subxiphoid level of an angiographic guide. Through angiographic guide is inserted a percutaneous transluminal angioplasty balloon catheter (PTA) into the pericardial cavity. Mechanical dilation of the balloon causes a dilaceration of pericardial opening, resulting in a pericardial window through which the drainage of pericardial space is done either in mediastinal space or in left pleural space or in peritoneal cavity.

This procedure can be considered as an alternative option for palliative therapy in critically ill patients or those at high surgical risk. The long-term prognosis of these patients depends mainly on their underlying malignant disease [20–22].

Subxiphoidal Pericardiotomy (Subxiphoidal Open Surgical Drainage)

Fenestration on the anterior face of pericardium is done by subxiphoid approach with local anesthesia or general anesthesia [1, 23]. Local anesthesia is preferable in patient with cardiac tamponade where general anesthesia may cause hemodynamic collapse and cardiac arrest by suppressing the sympathetic state.

An incision of 5–7 cm with subxiphoid approach is made, the white line is resected without opening the peritoneal cavity and the subxiphoidian appendage is resected. A small incision is made in the pericardium, at which point the intrapericardial fluid appears in the jet. Slow drainage of pericardial effusion prevents acute heart dilation. Liquid is harvested for cytological and biochemical examinations.

Fenestration is performed by excision of a 2/2 cm pericardial fragment that is sent for histopathological examination. The pericardial cavity is inspected in accessible area.

Place a drainage tube inferior and posterior to left ventricle, with tube exposing by counter-incision. Some authors recommend a second tube inserted on anterior heart.

Success rate exceeds 90%, morbidity is 10%, and mortality—0% [4].

The destruction of pericardial space through the inflammatory process triggered by the drainage tube appears to be the main factor in preventing relapse, a process more important than the initial fenestration.

Current technique of subxiphoidian pericardial window implies a median incision just inferior to the xiphoid process followed by the opening of white line with exposure of the superior aspect of the diaphragm cupola [24, 25]. The next step is removing the xiphoid process from the field either by hard retraction or by excision; this facilitates the access to pericardium. Then, the pericardium is opened and a small piece is taken for biopsy, followed by drainage of the fluid.

Left Paraxiphoidian Approach (Left Paraxiphoidian Open Surgical Drainage) (Cezar Motaș Procedure) [21]

The left paraxiphoidian approach of malignant pericarditis can be performed with local or general anesthesia, and is an easier access to the anterior face of pericardium without requiring the resection of xiphoid process (easier to perform with local anesthesia lidocaine 1% in these patients with cardiac tamponade).

After the median subcutaneous tissue incision with electrocautery, de-insert the insertion of the left rectus abdominal muscle from the xiphoid process, with access to the superior part of the diaphragmatic cupola, with exposing of the maximal pericardial bulge area (Fig. 2) [21]. The removal of pericardial fat allows direct visualization of the anterior pericardial face. Perform pericardial incision under visual control, with slow drainage of the pericardial fluid, and proceed for the pericardial biopsies (usually up to about 4 cm in diameter) (Fig. 3) [21]. Through this access path, perform endoscopic control of the pericardial space, perform intrapericardial drainage via counter-incision of a soft tube to minimize the risk of eventual cardiac wall damage [21].

Subxiphoid/Paraxiphoid Fenestration with Pericardoscopy

An important objective in malignant pericardial effusions is to establish the etiological diagnosis of pericardial effusion. Cytological examination of pericardial fluid and histopathological examination of pericardium fragments harvested from subxiphoidian window do not have maximum sensitivity [26]. Thus targeted pericardial biopsy by pericardioscopy was first described by Santos and Frater in 1977 [27].

To practice pericardoscopy, the patient should follow general anesthesia, which is a disadvantage. The method can only be applied to hemodynamically stable patients.

Access to the pericardial cavity is made by subxiphoidian or paraxiphoidian window, where the operative times are the same (Figs. 4, 5 and 6) [28].

Presently, there is no instrument dedicated to pericardoscopy (made by Storz, Olympus special equipment for pericardoscopy) because the existing instruments can be adapted: the thoracoscope (inserted through the pleural cavity for thoracoscopic pericardoscopy) or the mediastinoscope (inserted subxiphoid for subxiphoid pericardoscopy without opening the cavity pleural). Mediastinoscopes have several dimensions, the longest, 24 cm being preferred by Porte to make

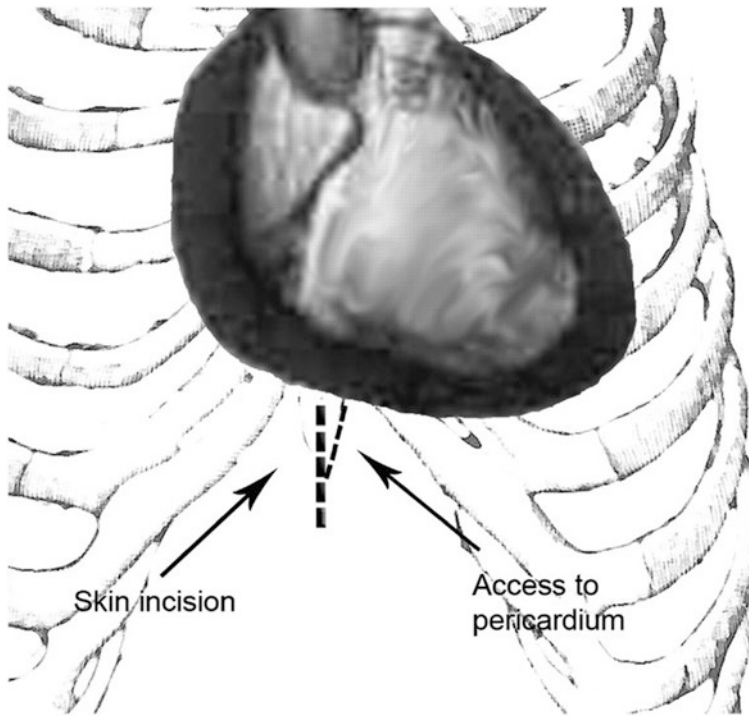

Fig. 2 Schematic presentation of the skin and paraxiphoidian incisions. From Ref. [21] with permission

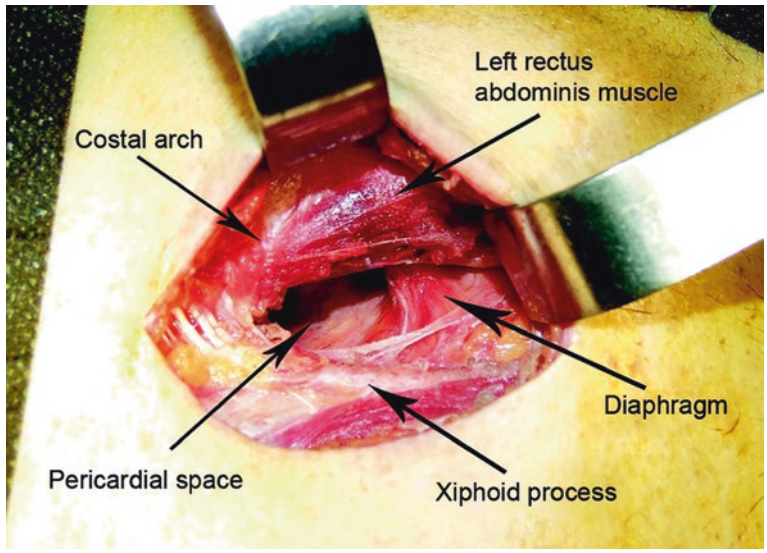

Fig. 3 Intraoperative aspect. From Ref. [21] with permission

subxiphoid pericardoscopy [4, 26, 29]. The pericardial cavity (fibrous pericardium and visceral pericardium) is inspected, targeted biopsies are taken from suspect areas (Fig. 7) [4, 26, 29].

When pericardoscope can be replaced with the telescope used by thoracoscopy, the endoscopic control, in addition to the biopsy, permits to evacuate the fibrinous deposits which are liable to obstruct the intrapericardial drainage tube and to make a pericardial window with scissors or by electrocautery [30]. After the dissection of the pericardium through subxiphoid approach we use a hybrid method of anterior pericardial fenestration using electrocautery and mechanical endostapler endo GIA (Claudiu Nistor procedure). Through this technique we perform a safe and fast 4 cm length pericardial fenestration under VATS control (Fig. 8).

During the procedure, up to 1/3 of patients have atrial or ventricular arrhythmias due to the myocardial mechanical irritation by the pericardoscope (thoracoscopy). Simple interruption of the exploration maneuver leads to the disappearance of arrythmia.

Only positive histological evidence has diagnostic relevance. A negative sample may be a false negative result, and there are hardly accessible areas for biopsy such as lateral wall of left ventricle.

Pericardoscopy is considered to be a procedure that is currently applicable, but is rarely used in practice (technical endowment, training).

Pleural—Pericardial Window

Creation of the pericardial-pleural window via antero-lateral thoracotomy through IV or V intercostal left space (open pericardial fenestration) is not longer justified because of high mortality—13% and post-operative morbidity of 35–67% [11, 31]. In some cases, in patients who do not tolerate selective intubation, a pleuro-pericardial window may be performed through a mini-toracotomy on the closest intercostal space to the inflated area of pericardium sac.

Same fenestration can be done by video-assisted thoracoscopic pericardial window surgery, achieving the following objectives: treatment or prophylaxis of cardiac tamponade, pericardial liquid harvesting for cytological and microbiological examination, sampling of pericardial tissue for histopathological examination, prophylaxis of fluid re-accumulation in

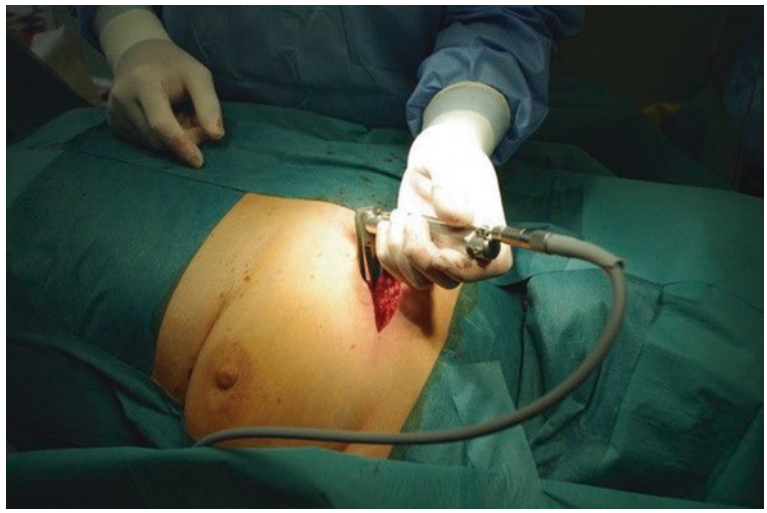

Fig. 4 The position of patient and the place of incision of left side mediastinoscope-controlled parasternal pericardial fenestration. From Ref. [28]

pericardium sac and pericardial constriction, and pleural biopsy [11, 31].

Pericardial-pleural fenestration through thoracoscopy (thoracoscopic pericardial fenestration) is performed on a patient able to undergo selective bronchial intubation (tracheal intubation using a double-lumen tube) with single-lung ventilation. The thoracotomy of necessity should be considered in case of a major intraoperative accident (damage of heart or coronary artery).

It is extremely dangerous to approach pericardium after pneumonectomy, as the newly created anatomical configuration and the fibrothorax are creating great technical difficulties, incidents and intraoperative accidents. In such situations, the pericardial-pleural window can be created by approaching the hemithorax with the remaining lung. Close cooperation between surgeon and anesthetist is required. The patient will be hyperoxygenated to support intermittent pulmonary ventilation.

Choosing the right or left hemithorax for the thoracoscopic approach of pericardial cavity is made depending on the part where the pericardial fluid is abundant or the side associated with pleural effusion. This is evidenced either by echocardiographic examination or by thoracic CT performed preoperatively. It intervenes on the pleural effusions side, and in case of bilateral pleural effusions, where the amount of fluid is higher. Contralaterally, a minimal pleurectomy will be made so that the patient can withstand ventilation on a single lung. In the absence of pleural effusion, the left thoracoscopic approach is preferred because it is easier to identify the phrenic nerve (which is located more anteriorly) and because there is found the ventricular heart muscle that is thicker, with a lower risk of damage during pericardial fenestration maneuvers. In contrast, on the right side is right atrium that has a thinner wall more susceptible to surgical lesion [11].

On the left side, the window may be made anterior or posterior to the phrenic nerve due to its median trajectory at the level of pericardium. On the right, the phrenic nerve is located more posteriorly in relation to the pulmonary hill so that the window can be made anterior to the phrenic nerve [11].

Surgeon stands behind the patient positioned in the lateral decubitus, facing the monitor screen. Surgical thoracoscopic surgery can be done uniportally or through two or three thoracoscopic ports. The three thoracoscopic ports are chosen as an inverse triangle in the lower third of thorax [11].

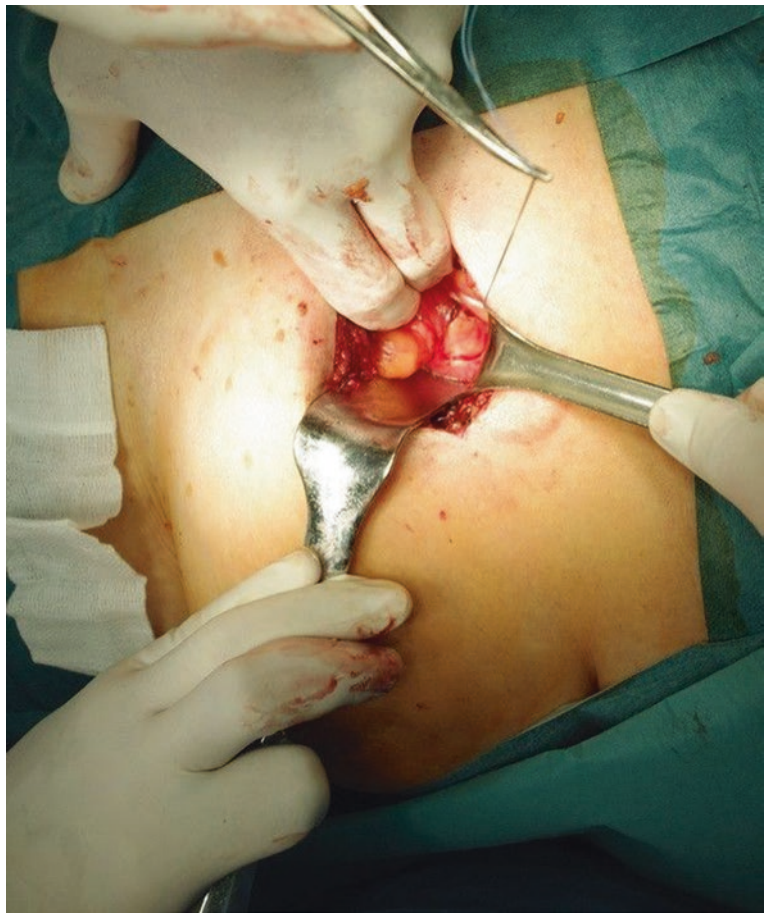

Fig. 5 The place of pericardial window (left side). From Ref. [28]

After exploring the pleural space, the phrenic nerve is identified. Depending on the location and trajectory of phrenic nerve, it is decided the place of pericardial fenestration, either anterior or posterior.

The hardest maneuver is to open the pericardium in tension. A pericardial puncture or a small electrocautery point may be performed, which will evacuate the liquid (Fig. 9).

It is time when heart can be damaged, more easily on the right side (right atrium with thin walls) or coronary arteries. After lowering the pericardial tension, the pericardium is caught with a tweezer and the fenestration is performed by the resection of a 3/3 cm pericardial fragment. The maneuver is carried out with the electric hook (Fig. 10), scissors or stapler—EndoGia (Fig. 11).

Pericardial fenestrations should be at least 3 cm^2 [11]. Some authors recommend a generous window of 15–30 cm^2, which at least on the right side may be a risk factor for herniation of the heart [32].

Pericardial fluid is collected for microbiological, cytological and biochemical examination. The resected pericardial fragment is kept for histopathological examination. It is also possible to harvest fragments of parietal pleura to determine neoplastic damage into the pleural space. The association of a malign pleural effusion also requires chemical or hybrid (chemical or mechanical) pleurodesis in order to prevent the recurrence of pleural effusion.

Thorax is drained with a single drain tube of 28 F or 32 F.

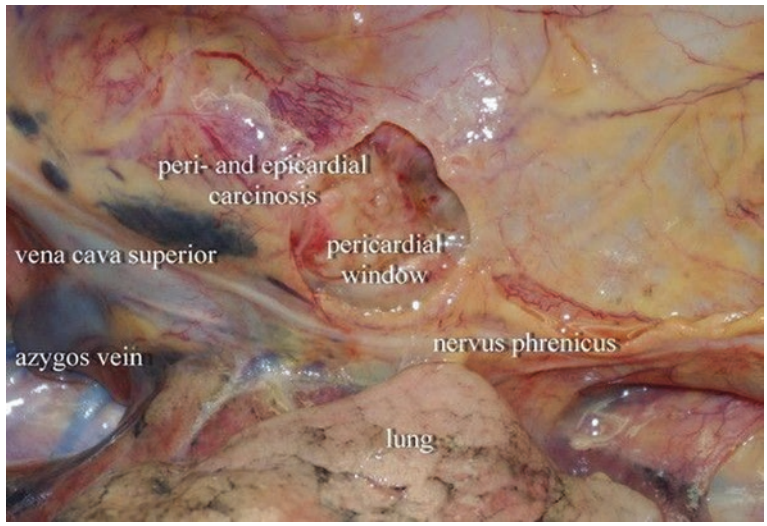

Fig. 6 The intrapleural situation after parasternal pericardial fenestration (right side). From Ref. [28]

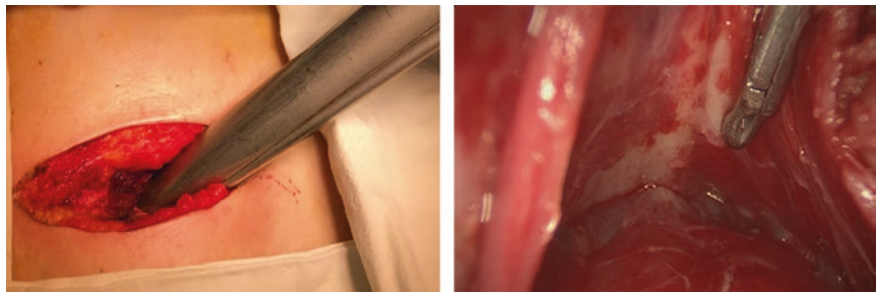

Fig. 7 Multiple biopsy of the pericardium by subxiphoid approach under endoscopic control (pericardoscopy)

During surgery, damage of the intercostal vessels, lung parenchyma, phrenic nerve or heart can occur. Damage of the heart requires repair of wounds by monofilament threads. Ventricular fibrillation is an incident that puts the patient's life in immediate danger. It may occur as a result of the contact between the monopolar electrocautery with the heart muscle. Some surgeons prefer bipolar electrocautery to perform pericardial resection. The risk of ventricular fibrillation requires the presence of an electric defibrillator available in the operating room.

On medium term, there is the risk of pericardial window obliteration with recurrence of malign pericardial effusion, especially in patients with associated pleurodesis, by fixation of the lung to the pericardial incision/window.

The mini-invasive pericardial-pleural fenestration is a preferred procedure for a stable patient, especially if it associates uni/bilateral pleural effusion [4, 33].

Peritoneal—Pericardial Window

Pericardial-peritoneal window is a variant of pericardial effusion drainage in patient with respiratory distress syndrome that does not support ventilation on a single lung and had a surgery on anterior inferior mediastinum and/or surgery on both pleural cavities.

The intervention is with general anesthesia with orotracheal intubation. Patients who do not support general anesthesia may also

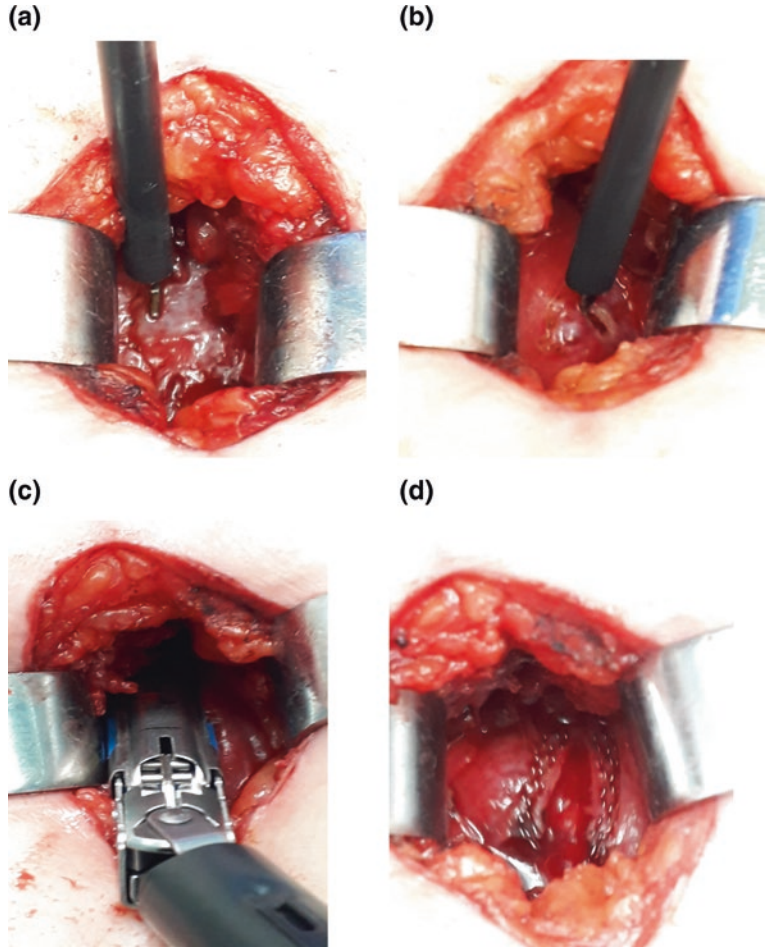

Fig. 8 Subxiphoid approach: process of creating an anterior pericardial window by hybrid method using both electric scalpel (a, b) and endostapler endoGIA (c,d) (Claudiu Nistor procedure)

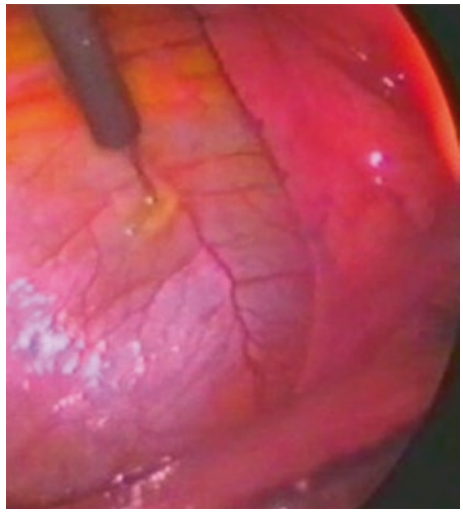

Fig. 9 Small puncture with electrocautery by through drainage of pericardial fluid is achieved

undergo local anesthesia. The incision is performed in the upper part of the epigastric region, with resection of the white line and the peritoneum, and then access into the peritoneal cavity. There is no need of resection of the xifoid appendix. The diaphragmatic central tendon is spotted which is pushed down due to intrapericardial fluid pressure. A small incision is practiced at this level (3–5 mm), fluid is evacuated slowly; samples for cytological, biochemical and bacteriological determinations will be collected.

After the partial drainage of pericardial effusion, the incision is extended vertically (3 cm), adding a transverse incision of the same length. This will result in a double phreno-pericardial

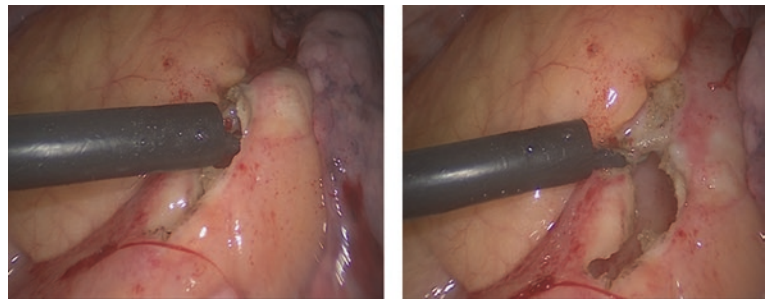

Fig. 10 **a** Process of creating a pericardial window with an electric scalpel. **b** Completion of pericardial window, which is 2–4 cm in diameter (VATS procedure)

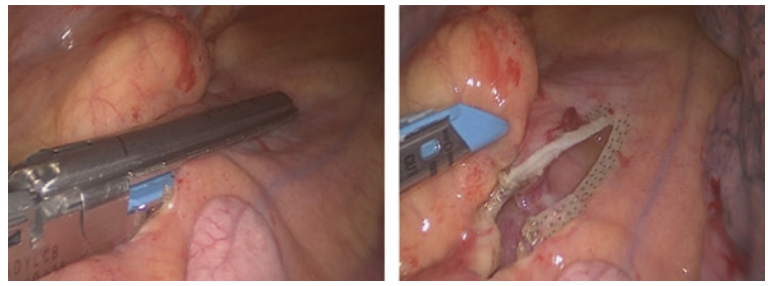

Fig. 11 Pericardial fenestration with endostapler EndoGia (VATS procedure)

incision in the form of a Greek cross Teodor Horvat procedure [9]. The upper and lower phreno-pericardial flaps, in number of four, are resected with histopathological samples. The final appearance of the pericardial-peritoneal window is a square. Inspect digitally and visually the pericardial cavity [9].

No pericardial or peritoneal cavity drainage is required. Finally, the abdominal wall is sutured into anatomical layers.

Pericardial-peritoneal fenestration can also be performed by mini-invasive laparoscopy (laparoscopic peritoneal-pericardial window).

"Closure" of the window may occur in the postoperative period by the left hepatic lobe which is platting the diaphragm or by intrapericardial herniation of the greater omentum, the small intestine or the transverse colon. The reverse herniation of the heart in the peritoneal cavity is unlikely if the technical execution standards are met.

To prevent these possible complications, a large mesh that would only allow the passage of the liquid could be mounted and would be a prophylactic barrier for the hernia.

Seeding the peritoneal cavity is a risk assumed with no prognostic importance in a patient with low survival expectancy.

An alternative to the pericardial-peritoneal window is pericardial-peritoneal Denver shunt, which ensures the unidirectional drainage of the fluid from pericardium to peritoneum [4].

Pericardiectomy

Partial or complete resection of the pericardium (Figs. 12 and 13) was a surgical procedure in the treatment of malignant pleural effusions, being performed by sternotomy or antero-lateral thoracotomy [34].

Although the success rate is significant—83.3%, the morbidity of 67% and a mortality of 13.3% makes pericardiectomy now a questionable indication [4]. The procedure may be discussed in case of failure of other surgical

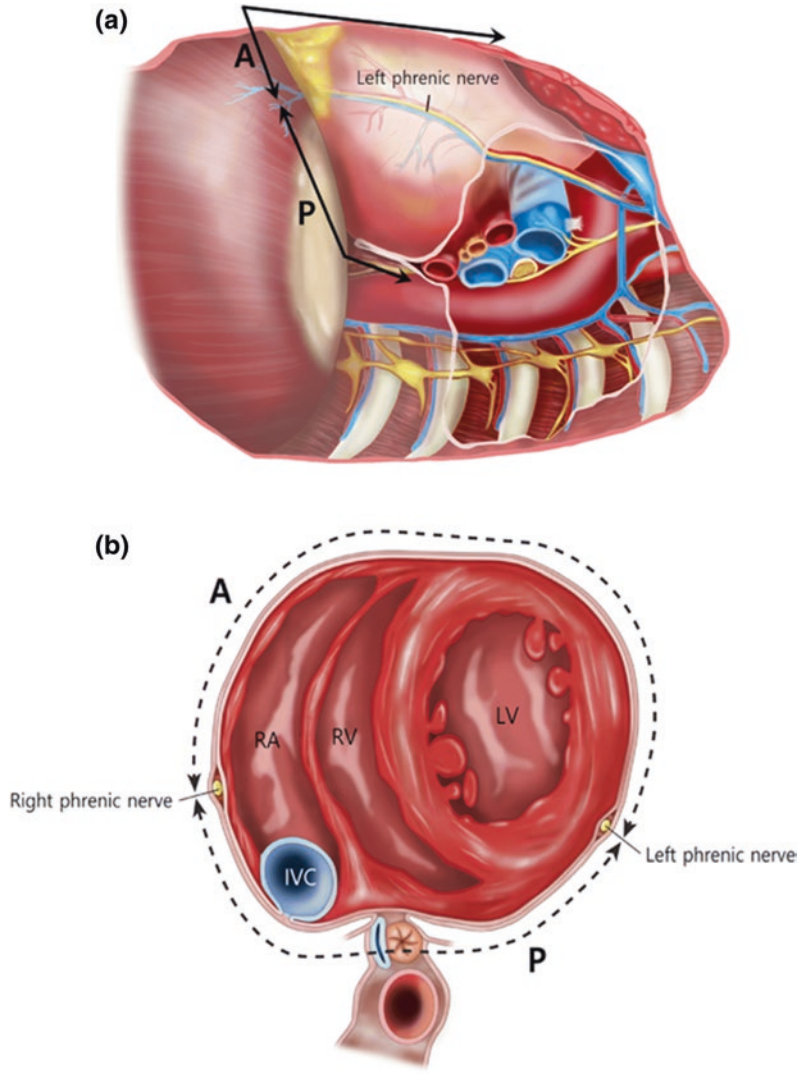

Fig. 12 Left lateral (**a**) and axial view (**b**) of the heart. The range of conventional pericardiectomy was A and that of radical pericardiectomy was A and P. (A, pericardium anterior to phrenic nerve; IVC, inferior vena cava; LV, left ventricle; P, pericardium posterior to phrenic nerve; RA, right ventricle; RV, right ventricle). From Ref. [34]

procedures, when it is preferable to be performed with minimal invasive procedure [32].

Pericardiectomy is particularly indicated in the case of direct invasion of the pericardium by a neighboring tumor process (bronchopulmonary cancer, diffuse pleural mesothelioma, mediastinum tumor, anterior thoracic wall tumor). Under these circumstances, pericardial resection is an operation associated with other resections of thorax (resection of lung or pleural-pulmonary resections, resection of mediastinal tumor etc.) and it is practiced respecting oncological principles.

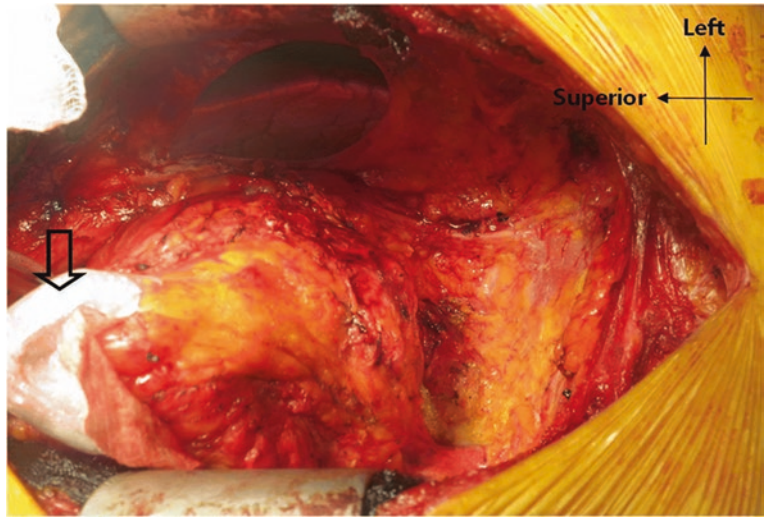

Fig. 13 Radical pericardiectomy resects the pericardium until the inferior vena cava, coronary sinus and pulmonary veins are seen. A cardiac positioner (arrow) is useful to retract the heart. From Ref. [34]

Pericardial reconstruction (pericardoplasty) has absolute indication after right pericardectomy to prevent herniation of the heart and squeezing or clamping of the veins cave (risk of cardiac arrest).

Following left pericardiectomy, there is no risk of veins cave clamping or squeezing. In small and medium pericardial defects with no pericardoplasty, there is the possibility of squeezing of the cardiac wall by the edges of the lesion. To prevent myocardial infarction caused by stopping the coronary circulation, there are two options: widening of the pericardial breach or pericardoplasty with mesh. Complete herniation of heart in left thoracic cavity, although it does not have immediate haemodynamic consequences, may lead to cardiac constriction that is caused by fibrothorax.

After anterior pericardiectomy, theoretically there is no risk of heart herniation; the risk is potential if it is associated with resection of mediastinal tumor or with anterior parietectomy and a pulmonary resection, especially on right or sometimes on left side.

There are authors who make the pericardoplasty on the right, respectively left and randomly after the anterior pericardectomy.

Pericardoplasty should achieve 4 goals: (1) heart herniation prophylaxis, (2) heart protection, (3) prophylaxis of fluid accumulation and (4) cardiac constriction.

Prognosis

The immediate prognosis of malignant pericardial effusions is influenced by the risk of postoperative low cardiac output (PLCO).

Postoperative low cardiac output does not appear to be influenced by the nature of the pericardial effusion (malignant, paraneoplastic or benign), but its causes are being clarified.

A number of risk factors have been implicated: direct damage to the myocardium by the tumor, myocardial ischemia during cardiac tamponade, toxic effect of myocardial cytostatics and anesthetics, prolonged myocardial stunning/hibernation and rapid pericardial decompression [35].

Postoperative low cardiac output is the leading cause of early mortality in patients with pericardial effusions.

Cardiac monitoring and inotropic support are required to overcome the critical moment.

The late prognosis is closely related to the type of malignant tumor, which caused the malignant pericardial effusion.

Thus, survival is greater in lymphomas (20.4 months) than in other malignant tumors (4.9 months) [35]. And from the latter, breast cancer has a better prognosis (8.3 months) [5].

The surgical procedure does not influence survival in malignant pericardial effusions.

Self-study

1. Which statement is/are true:
   a. Pericardiocentesis is the percutaneous technique of pericardial drainage that is performed under local anesthesia.
   b. Pericardiocentesis is indicated in emergency situations when malignant pericardial effusion is complicated by cardiac tamponade phenomena.
   c. Pericardiocentesis is not without risks, cardiac wall or coronary artery can be damaged, or major arrhythmia may occur.
   d. Pericardiocentesis drainage of more than 1 L of pericardial fluid should be avoided.

2. Which statement are true:
   a. Pericardial-pleural fenestration through thoracoscopy is performed on a patient able to undergo selective bronchial intubation with single-lung ventilation.
   b. The mini-invasive pericardial-pleural fenestration is a preferred procedure for a stable patient, especially if it associates uni/bilateral pleural effusion.
   c. Pericardial-peritoneal window is a variant of pericardial effusion drainage in patient with respiratory distress syndrome that does not support ventilation on a single lung and had a surgery on anterior inferior mediastinum and/or surgery on both pleural cavities.
   d. Pericardial-peritoneal fenestration can also be performed by mini-invasive laparoscopy.

Answers

1. Which statement is/are true:
   a. CORRECT
   b. CORRECT
   c. CORRECT
   d. CORRECT

2. Which statement are true:
   a. CORRECT
   b. CORRECT
   c. CORRECT
   d. CORRECT

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Inflammatory Pericardial Effusion

Tanıl Özer, Mehmet Aksüt, and Kaan Kırali

Key Points

1. Anti-inflammatory therapy should be considered at inflammatory pericardial effusions.
2. Pericardiocentesis or tube drainage should be performed immediately when cardiac tamponade occurred.
3. Pericardiectomy may be considered when presence of recurrent pericardial effusion.
4. Subksifoidal or trans-thoracic pericardial window approaches may be preferred as a less invasive technique when pericardiectomy is concerned.

Introduction

The pericardium is a fibrous and serous sac surrounding the heart and the roots of great vessels. The fibrous part behaves as a barrier that isolates the heart from other mediastinal and intra-thoracic structures. The serous component of pericardium has two layers. External layer, which is called parietal pericardium, covers inner face of fibrous part. Internal layer, which is called visceral pericardium or epicardium, is under strong relationship with myocardium (Fig. 1). These two continuous layers separated by a cavity containing 10–50 ml serous fluid. Since a slippery surface created by this serous fluid, the layers can move without rubbing each other while the heart beating [1–3]. Some conditions cause an increment of the fluid amount and change the character of fluid (e.g. exudate, blood, pus etc.). In such case, the fluid inside pericardium is called pericardial effusion.

Pericardial effusions have several classifications. These classifications are related to its onset, size, hemodynamic effect, distribution, composition of the fluid (Table 1). Besides, treatment strategies do alter at different situations. Thus, urgent drainage of effusion is often life saving on acute situations, while subacute and chronic pericardial effusions rarely need [4, 5].

Clinical Presentation

The clinical presentation of pericardial effusion mainly depends on its etiology. Presentation of a pericardial effusion case may differ from incidental finding without any symptom to circulatory collapse situation. In the pericardial space, fluid accumulation speed has an important effect on hemodynamic response. The relatively non-compliant environment created by pericardium

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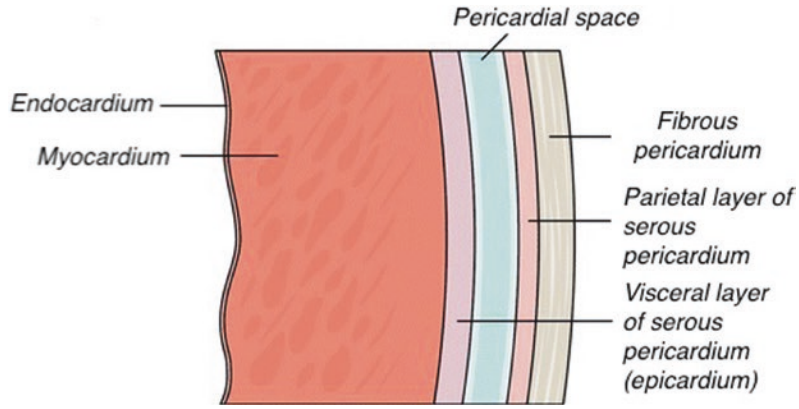

Fig. 1 Pericardial layers

Table 1 Classification of pericardial effusion

Onset	Acute (<1 week) Subacute (1–12 weeks) Chronic (>12 weeks)
Size	Mild (<10 mm thickness or 50–100 ml) Moderate (10–20 mm thickness or 100–500 ml) Large (>20 mm thickness or >500 ml)
Hemodynamic effect	Without cardiac tamponade With cardiac tamponade Effusive-constructive
Distribution	Circumferential Loculated
Composition of fluid	Transudate Exudate Hydropericardium Hemopericardium Chylopericardium Pyopericardium Pnumopericardium

forms a nonlinear relationship between intra-pericardial pressure and intra-pericardial volume (Fig. 2). A small increment in fluid volume in minutes may cause serious decrease on cardiac output. Conversely, slow accumulation in the pericardial cavity do not causes noteworthy increase in intra-pericardial pressure even large volumes are concerned [1, 6, 7].

Symptoms and signs of pericardial effusion are not sensitive or specific to effusion. Patients who are not hemodynamically effected by pericardial effusion admit to hospital with nonspecific symptoms associated with underlying disease (e.g. fever, fatigue, anorexia, nausea and vomiting …) or indirectly occurred symptoms due to local compression of effusion (e.g. dysphagia, hoarseness, cough, hiccups …) [8, 9].

When effusion exceeds the pericardial stretching limit, pericardium looses its ability to accommodate intra-pericardial pressure. Hence, hemodynamic effects begin to emerge (Fig. 3). The cascade which starts with elevation of intra-pericardial pressure results with decrease of cardiac output. Consequently, the symptoms as like dyspnea and orthopnea related to low cardiac output syndrome reveal. Especially for acute situations, Beck Triad was identified. This triad includes hypotension, increased jugular venous pressure, and quite heart [10].

Especially inflammatory pericardial effusions cause chest pain due to pericardial irritation. Moreover, palpitation, fullness are other symptoms that patients also complain.

Any noteworthy sign may not be found at physical examination while absence of hemodynamic deterioration. Cardiac sounds may be heard diminished on auscultation due to increased pericardial fluid. If inflammatory effusion is present, a friction rub sound may be heard while the pericardial layers move at every heart beat. Therewithal, there is no exact correlation between effusion size and pericardial rub. Electrocardiographic findings may include decrease of QRS complex voltage, elevation of ST segment and depression of PR segment. ST

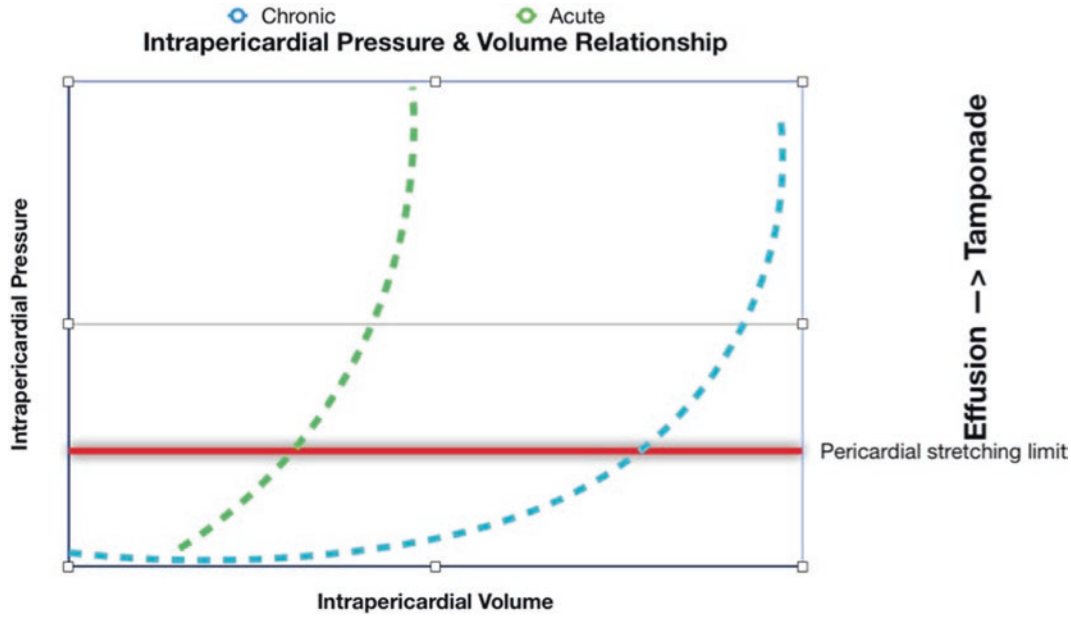

Fig. 2 Relationship between intra-pericardial pressure and volume

elevation and PR depression on ECG are especially seen when acute pericarditis is present. Moreover, this situation may imitate acute coronary syndrome which should be excluded by coronary angiography [11–13].

Chest X-ray is recommended when a suspicious pericardial effusion case is present due to become an easy and fast way for the initial evaluation [2]. Although it is recommended, chest X-ray has low sensitivity and specificity to diagnose pericardial effusion. Small and moderate effusions may not create a significant change on chest X-ray while larger effusions enlarge the cardiac silhouette and increase the cardio thoracic index. Additionally, when an isolated left sided pleural effusion without any other explaining situation is seen, inflammatory pericardial disease may be consider [14].

Echocardiography is required to clarify the suspicious diagnosis of pericardial effusion. Also, it can provide noteworthy information regarding to hemodynamic impact of effusion [5, 7]. Effusion size and its hemodynamic importance are firstly evaluated by echocardiographic assessment. Swinging heart may be seen inside the moderate and large effusion. Diastolic collapse, respiratory variation of mitral and tricuspid flow, dilatation of inferior vena cava and presence of plethora (less than 50% reduction of VCI diameter with inspiration) are valuable signs to diagnose cardiac tamponade [15]. When trans-thoracic echocardiography (TTE) does not provide sufficient view to assess the pericardial effusion, transesophageal echocardiography (TEE), which is more invasive method than TTE, may be preferred [16].

Although echocardiography still remains significant to initial diagnose for most of pericardial effusion cases, computerized tomography (CT) and cardiac magnetic rezonans (CMR) may be enlightening to the cases which echocardiography remains insufficient. Especially revealing the loculated pericardial effusion, pericardial thickening and masses, characterizing the nature of effusion, CT and CMR are helpful to diagnose the effusion and determine the underlying pathology [17, 18].

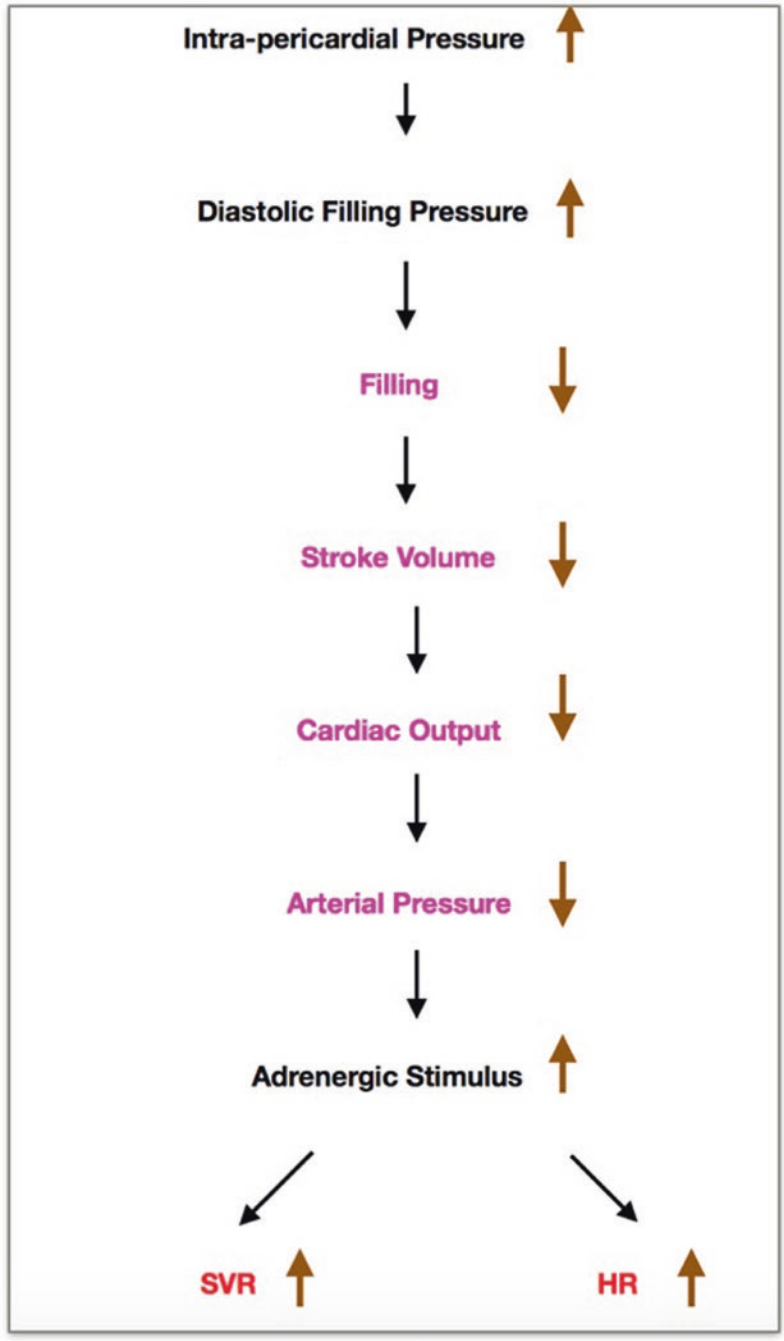

Fig. 3 Increase of intra-pericardial pressure

Etiology

The etiological factor of pericardial effusion varies according to the local epidemiological differences. In developed countries, the most common etiological factor is idiopathic or viral pericarditis. On the other hand, tuberculosis still remains the most common etiological agent in developing countries. The etiological factor of inflammatory pericardial effusion may vary depending on infectious or non-infectious origin (Table 2) [19].

Histologic, cytologic, immunohistologic evaluation, detection of viral DNA/RNA are required for definitive diagnosis of viral pericarditis. But, the necessity of these test are very rare. Moreover, performing of routine viral serologic tests are not recommended except human immunodeficiency virus (HIV) or hepatitis C virus (HCV) [2, 20, 21].

Pericardial effusion originated from bacterial agent is uncommon in the developed countries whereas mycobacterium tuberculosis is still remains the most common agent which causes pericarditis in the developing countries. Tuberculosis is found as an etiological agent of more than 50% patients who has diagnosed pericardial effusion in developing countries [22]. Other bacterial agents are uncommon in both developed and developing countries. Definition of the bacterial agents requires evaluation of pericardial fluid samples. Furthermore, other uncommon agent as like funguses and protozoans may be responsible for inflammatory pericardial effusion especially when immunosuppression is present [23].

The involvement of pericardial layers may be seen in the systemic auto-immune diseases and metabolic disorders. But this involvement is not common and the complaints are nonspecific. The most commonly seen auto-immune diseases are systemic lupus erythematosus, Sjögren's Syndrome, rheumatoid arthritis, and scleroderma. Uremic pericarditis occurs by the toxins related inflammatory response in the renal failure patients.

The injuries of pericardial and/or myocardial tissues cause an inflammatory response on pericardium. These injuries may be caused by sharp/blunt traumas or ischemic situations (Dressler Syndrome) and the inflammatory response occurs a few week later initial case occurred.

Treatment Strategies

Treatment strategies are mainly related to onset of pericardial effusion. Acute accumulated pericardial effusion should be intervene urgently to decrease the intra-pericardial pressure. Additional medical therapy involves anti-inflammatory drugs mainly, and commonly empiric start is preferred especially at inflammatory pericardial effusions.

Table 2 Etiological factors of inflammatory pericardial effusions

Infectious	Non-infectious
Viral Enteroviruses (echoviruses, coxsackie B) Influenza, EBV, CMV, Adenovirus, Varicella, Rubella, Mumps, Hepatit viruses, Parvovirus B19, HHP	*Auto-immune* SLE, Sjögren Syndrome, rheumatoid arthritis, systemic sclerosis, systemic vasculitis, Behçet Syndrome, sarcoidosis, FMF, Churg–Strauss Syndrome
Bacterial Tuberculosis, Coxiella burnetii, Pneumococcosis, Meningococcosis, Gonococcosis, Haemophilus, Staphylococci, Chlamydia, Mycoplasma, Legionella, Leptospira, Listeria	*Pericardial injury syndrome (Dressler Syndrome)* Post-MI, post-pericardiotomy, post-traumatic
Fungal Histoplasma, Aspergillosis, Blastomycosis, Candida	*Metabolic* Uremic pericarditis
Protozoal Echinococcus, Toxoplasma	*Drugs and toxins*

EBV Epstein-Barr Virus, *CMV* Cytomegalovirus, *HHP* Human Herpes Virus, *SLE* Systemic Lupus Erythematosus, *FMF* Familial Mediterranean Fever, *MI* myocardial infarction

Other than onset of pericardial effusion, underlying disease, size of effusion and recurrency status are the important issues that need to be considered to manage the treatment. Anti-infective and anti-inflammatory drugs should be targeted to main etiological diagnosis. Although medical treatment of pericardial effusion has no strong recommendation, these therapies may start as an empiric therapy [2]. If medical therapy is not successful to reduce the effusion, interventional approaches should be considered for both therapeutic and diagnostic proposal.

Pericardial Drainage

Although drainage of pericardial effusion is often performed for therapeutic purposes, it may also be performed to clarify the diagnosis by molecular, histologic and microbiologic assessing the fluid sample or pericardial tissue [24]. According to clinical experiences, pericardiocentesis or subxiphoidal surgical approaches can be preferred for drainage of pericardial effusion. Both techniques can be done in urgent and elective situations by experienced staffs.

Pericardiocentesis can be done safely under echocardiography or fluoroscopy guidance from either subxiphoid or transthoracic parasternal areas with local anesthesia. Blind applications must be avoided not to increase the risk of cause an injury on the other nearby placed organs.

The catheter which is placed into pericardial sac through locally anesthetized subxiphoid area must be directed to left shoulder. Then a pigtail catheter is placed to where the effusion is the highest amount. When parasternal area is to be used for access route, puncture must be done at fourth intercostal space, 3–5 cm away from the sternal edge to prevent internal thoracic artery injury. Another trick to do safer drainage with pericardiocentesis is to state the closest part of the effusion to skin. If the effusion located posterior or lateral position, accumulated fluid is not free and adhesions are present or if the effusion <10 mm; pericardiocentesis is not appropriate. Prolonged drainage with pericardiocentesis of up to 30 ml/24 h may be considered in order to prevent re-accumulation [25].

Pericardial tube drainage is performed with subxiphoidal incisions and includes aspiration of pericardial fluid and placing drains inside the pericardial sac. Surgical approach must be considered when the fluid is loculated, posteriorly or laterally placed. Additionally pericardial biopsy can be taken with this approach if the diagnosis is unclear or any suspicious event is present. This approach can be performed by either general anesthesia or simple local anesthesia. A 5–6 cm longitudinal incision is made just below the xiphoid process and the pericardium explored. After opening the pericardial sac an aspirator is gently put inside the sac with lean on the pericardial layer. A drain is left inside the pericardial sac through this iatrogenic space to let the remnant fluid drainage continue before the layers are closed again (Fig. 4). The tube must be left inside the pericardial sac, till the drainage decrease down to 100 ml/24 h [26].

Pericardial Window

Pericardial window especially is performed when the re-accumulation is occurred and can also be done subxiphoidal or trans-pleural approaches. Subxiphoidal pericardial window is very similar to subxiphoidal tube drainage. Main differences are the suturing of fibrous pericardial layer to subcutaneous tissue and making a little hole to peritoneum without leaving any tube inside the pericardial space. Thus intra-pericardial fluid can pass into peritoneal cavity and cardiac tamponade can be prevented.

Trans-pleural approach can be done by either thoracotomy or video-assisted thoracoscopy. With pericardia-pleural opening, intra-pericardial fluid passes to pleural cavity. An anterolateral thoracotomy is done from the fourth intercostal space and a sufficient pericardial tissue resection is made anterior the phrenic nerve. Same resection can be made by video-assisted thoracoscopy.

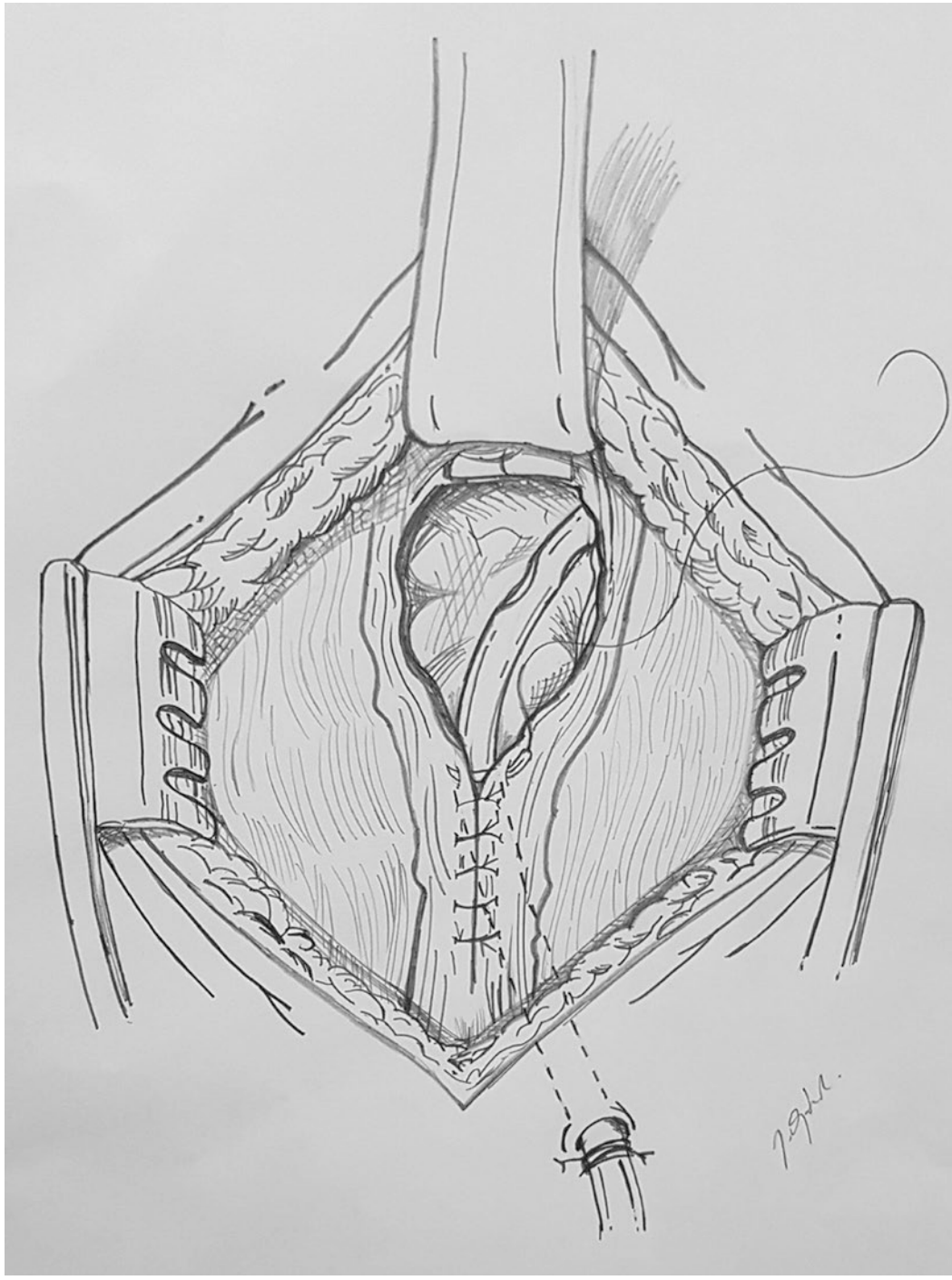

Fig. 4 Pericardial tube drainage

These two approaches also can be done by percutaneous balloon pericardiotomy [27]. Pericardial window is commonly performed for palliative therapy especially on the patient whose life expectancy is low [2].

Pericardiectomy

When the procedures above mentioned do not seem appropriate or sufficient, pericardial resection and decortication via full sternotomy may be considered. Although pericardiectomy is considered for refractory pericardial effusions, more commonly performed for surgical treatment of constrictive pericarditis. Actually, isolated pericardial effusion cases, whether inflammatory or not, occasionally goes to pericardiectomy which is differentiated according to resected part of pericardium. While mentioning pericardietomy, most commonly, the resection of anterior pericardium which lies between both phrenic nerves is meant. If it is called radical pericardiectomy, additionally posterior and diaphragmatic pericardial resection is done.

While pericardiectomy can be performed by full sternotomy, bilateral thoracotomy or thoracosternotomy (Clamshell incision) can also be used. The most important issue during resection is accurately sorting the resecting part of pericardium. The resection always must start from aorta and left ventricle, then goes on to pulmonary artery and right ventricle. If this rule is broken, sudden increased preload cannot be compensated by left ventricle and so acute pulmonary edema and right heart failure become inevitable.

Conclusion

Pericardial effusion may occur due to any cause. Increased systemic inflammatory parameters suggest the inflammatory effusion and so empiric anti-inflammatory drugs may be used for treatment. Acute accumulation and large effusions necessitate to intervene urgently for both treatment and diagnostic purposes. Pericardial window opening procedures, especially for isolated effusions, may be preferable approaches rather than pericardiectomy.

Self-study

(1)Which sentence is incorrect?
- (a) Empiric anti-inflammatory treatment may be used when the etiology is unclear.
- (b) Pericardiocentesis may be the first choice in the case of cardiac tamponade.
- (c) Pericardial tube drainage may be the first choice in the case of cardiac tamponade.
- (d) Pericardiectomy may be the first choice in the case of cardiac tamponade.
- (e) Pericardial window opening is performed when recurrent pericardial effusion is present.

(2)Which situation is not appropriate for percutaneous pericardiocentesis?
- (a) Located posterior or lateral position
- (b) Presenting adhesions
- (c) Lesser than 10 mm effusions
- (d) Septate effusions
- (e) All

Answers

(1)d
(2)e

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Pericardial Tumors

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Key Points

- Methastatic invasion of the pericardium is common in the neoplastic patients but the primary pericardial tumor prevalence is very low.
- The most common primary pericardial tumors are pericardial cyst, lipoma, teratoma and mesothelioma. Carcinomas of the lung and breast are the most common secondary pericardial tumors.
- Symptoms are atypical and usually occurs due to the cardiac compression.
- Surgical resection is usually required but the prognosis is bad in malignant pericardial tumors.

Introduction

General

Pericardial tumors are very rare seen pathologies. Prevalence of the primary pericardial lesion is reported as up to 0.007% and only 12.8% of the tumors in the pericardiac region arises at pericardium [1]. Beside of this, secondary pericardial tumors are 1000 times more common [2]. Secondary tumors have malignant characteristics and the most common type is carcinoma and lymphoma [3]. In primary pericardial tumors, the rate of benign/malignant was reported to be 1/1 [4]. The most common benign tumors of the pericardium are pericardial cyst and lipoma. The most common primary pericardial neoplasm is mesothelioma [2].

Although primary pericardial tumors are very rare, pericardial metastases have been reported in nearly 15.4% of patients who died due to neoplasm in their autopsy series [5]. Metastases to the pericardium usually occur through lymphatic and direct invasion. On the other hand, the metastases to the heart are mostly hematogenous. Pericardiac metastasis is an indicator of poor prognosis and results in death within 4–12 months [4]. The most common secondary tumors of pericardium are lung and breast carcinoma, lymphomas and melanomas, respectively [3, 5]. Primary and secondary pericardial tumors are summarized in Table 1.

Primary pericardial tumors may remain asymptomatic for a long time until complications develop. In benign tumors complications occur due to the compression. In malignancies, inflammation may result in pericardial effusion and tamponade. Pericardial effusion is generally hemorrhagic and occurs in 2/3 of malignant

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Table 1 Pericardial tumors

	Primary pericardial tumors	Secondary pericardial tumors
Benign	Pericardial cyst	
	Lipoma	
	Teratoma	
	Angioma (hemangioma)	
	Paraganglioma	
Malignant	Mesothelioma	Carcinomas
	Pericardial sarcoma	1. Lung
	1. Angiosarcoma	2. Breast
	2. Synovial sarcoma	3. Esophageal
	3. Liposarcoma	Melanoma
		Leukemia
		Lymphoma

pericardial tumors [4]. The symptoms do not differ according to the tumor type and are usually atypical. There are similar findings to heart failure. The most common symptoms are dyspnea (51%), weight loss (20%), chest pain (17.1%), edema, cough, palpitations, sweating and fever [6].

Anatomy and Hystology

Pericardium is a double-layered structure that surrounds whole around the heart. The outer layer is called parietal pericardium and the inner layer is called visceral pericardium (epicardium). The parietal pericardium is composed of a thick, fibrous layer rich in connective tissue and a thin serous layer coating its inner surface. This serous layer is folded over at the edges of the pericardium, covers the entire heart and adhered directly to the myocardium. The serous layer over the myocardium is called epicardium and consists of the single-story mesothelial cells. Epicardium and the serous layer on the inner surface of the parietal pericardium are the continuation of each other. The space between the two serous layers is called the pericardial space and there is up to 50 ml of serous fluid secreted from these serous layers. This serous fluid acts as a barrier to soften traumas and jolts. Fibrous part (the outer layer of the parietal pericardium) maintains the heart's anatomical position and its geometric shape. Fibrous part consists of a small amount of elastic lamella and a large amount of collagen fiber-containing connective tissue. Fat tissue is hardly ever seen in pericardium at newborns but increases in both epicardium and pericardium as age grows [7]. Lymphatic drainage of both layers of the pericardium is performed on separate pathways. Epicardial lymphatic drainage occurs to the tracheal and peribronchial lymph nodes. Lymphatic drainage of the anterior side of the parietal percardium occurs into the anterior mediastinal lymph nodes while the lateral and posterior sides are drained into the posterior mediastinal lymph nodes. The arterial supply of the pericardium arrives from the pericardiophrenic and musculophrenic arteries, which are internal mammarian artery branches. Venous drainage occurs with pericardiophrenic and inferior phrenic veins [8].

Diagnosis

Imaging techniques play an important role in detecting tumors and determining tumor type. The prevalence of pericardiac tumor has been reported to be increased with the advancement of imaging technology. There was an increase in the incidence of primary cardiac tumors from 0.06% in the early 1980s to 0.32% between 1990 and 1995 [9]. Diagnosis process of the pericardial tumors begins with plain radiography of the chest. Radiographic findings include an enlarged cardiac silhouette, an abnormal mediastinal contour, or a discrete mediastinal mass [1, 2]. Another non-invasive imaging technique, echocardiography, helps in imaging tumors, monitoring pericardial effusion, and helps minimally invasive pericardial sampling. Although non-invasive techniques are frequently used, CT and MRI are the main diagnostic methods for diagnosis. CT is effective in evaluating the localization of the tumor site and neighborhoods. CT also narrows the differential diagnosis by attenuation value or pattern of enhancement characteristics of tumors [2]. In metastatic pericardial

tumors, the origin is frequently intrathoracic neoplasms and CT was the most frequently used method for the diagnosis of these tumors. Electrocardiography (EKG) gated CT reduces the artifacts and may have superiority but has not been proven yet [5]. MRI is superior to CT in imaging soft tissues. Because of the characteristic appearance of tumors, MRI may be more helpful in diagnose. It shows myocardial or and surrounding tissue invasions more clearly due to it's high resolution. Despite the many advantages of MRI imaging, usage of CT is more common [6]. Positron emission tomography computed tomography (PET-CT) is another recommended imaging method in metastatic pathologies for detecting the spread and primary lesion.

Pericardial tumors have many non-specific radiological findings. Pericardial effusion and pericardial thickening are the most common radiological findings [2]. Although pericardial effusion has been reported with a frequency of 90% in some series. It is usually caused by non-malignant atiologies (e.g. radiation pericarditis or opportunustic infections) in neoplastic patients [5]. The effusion is usually hemorrhagic if it is associated with malignancy [4]. Serous effusions are usually seen in benign pathologies as well as in malignant pathologies [2, 4]. Over 4 mm parietal pericardial thickness is defined as pericardial thickening [10]. Pericardial thickening usually tends to be diffuse type (%66). Local pericardial thickening occurs in nodular manner and most commonly be seen in the epicardium over the right ventricular anterior free wall (%18). Other common sites are the pericardium over the right ventricular outflow tract, the left ventricular surface and the left atrioventricular groove [5]. The presence of a pericardial nodule indicates metastatic pericardial involvement and secondary pericardial tumor existence [11]. Pericardial nodules are most commonly seen in the pericardium over right anterior free wall [5]. Although imaging methods narrow the differential diagnosis, sampling and histopathological studies are required to confirm the diagnosis and treatment management [2, 3, 10, 12]. Pericardiocentesis and pericardial biopsy procedures are usually performed under the guidance of echocardiography. Successful results have also been reported with CT-guided mediastinal biopsy [13]. Reported specificity of cytologic analysis has ranged from 27 to 93%. The success and sensitivity of echocardiography-guided pericardial biopsy has been reported as 27–65% in some series [14]. Pericardoscopy-guided pericardial biopsies revealed a higher rate of diagnosis (93–97%). Therefore, it is recommended to use pericardioscopy for biopsy procedures [14].

Pericardial tumors will be described under two main headings: primary pericardial tumors and seconder pericardial tumors.

Primary Pericardial Tumors

Benign Pericardial Tumors

Pericardial Cyst

The most common type of benign pericardial mass is the pericardial cyst. There are different types of pericardial cysts. Congenital pericardial cysts are discussed in this chapter as pericardial cysts. Other types of pericardial cysts are inflammatory cysts caused by inflammation, bacterial infection or trauma and Hydatid cysts are caused by Echinococcus granulosus [10].

Congenital pericardial cysts also called mesothelial cysts are an aberrant formation of the somatic cavities and are usually unilocular [2]. Right and left anterior cardiophrenic angles are the most common locations of these cysts. Histology analysis reveal that cyst walls consist of connective tissue rich in collagen fibers and the inner surface is covered by a single layer of mesothelial cells the same as pericardium. Fluid in the cyst is mostly serous [15]. Pericardial cysts are usually asymptomatic and found incidentally on chest X-RAYs or echocardiography. Smooth anterior mediastinal mass can be seen in plain chest radiographies. Echocardiography demonstrates the cystic nature of the mass [2].

CT or MRI is often needed [10]. At CT imaging, pericardial cyst appears as a well defined, non-enhancing, homogeneous fluid-attenuation lesion that contains no internal septa [2]. Occasionally cysts are complicated by infection or trauma. As a result of this, cystic fluid becomes proteinaceous or hemorrhagic. MRI provides better information about the internal contents of the cysts. Normally, pericardial cysts demonstrate intermediate to low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. Pericardial cysts with proteinaceous content show high signal intensity with T1-weighted sequences and intermediate to low signal intensity with T2-weighted sequences. Hemorrhagic cysts are hyperintense with T1-weighted sequences and demonstrate susceptibility with gradient recalled echo sequences [2].

Treatment is not necessary in asymptomatic congenital cysts. In symptomatic cases, percutaneous aspiration and sclerosis by ethanol instillation can be done. If this is not feasible surgical resection may be necessary [10].

Lipoma

Lipomas are benign lesions and usually occur in the heart especially subendocardium, at pericardiac regions [16]. Incidence does not depend on age and gender [6, 17]. Pericardial lipomas are encapsulated, hystologically composed of mature fat cells with a small fibrous connective tissue, similar to lipomas originating from other regions [6]. The shape of a pericardial lipoma is determined by the space they occupy [2]. Pericardial lipomas usually have an echogenic appearance at echocardiographic analysis. These lesions demonstrate homogeneously low attenuation below 0 HU and do not enhance with the contrast material administration. MRI can be used to further characterize the tumor and reveals the extent of lesions by fat-suppression techniques. On T1-weighted sequences, lesion appear as homogeneously hyperintense and does not enhance [2, 6]. They usually occur singly but multiple tumors can be seen, particularly in the setting of tuberous sclerosis [18]. Invasion of the myocardium was reported rarely [19]. In asemptomatic patients intervention is not required.

Teratoma

Teratomas are germ cell tumors and are derived from two or three germinal layers [2, 6, 12, 15]. Endodermal, ectodermal and mesodermal cellular components were visible at histological analysis [15]. The tumor is generally a multilocular cystic mass located at the right anterior side of the pericardium and attached by a fibrous pedicle. Nearly all of the lesions at the pericardiac region arise in the pericardium [20]. Although malignant cases were reported, teratomas are mostly benign and not invasive [6, 12]. But they tend to grow rapidly and can have serious mechanical consequences because they mostly occur during fetal period or infancy. There is a risk of fetal or neonatal death because fetal hidrops can develop during in utero period [21]. Diagnosis is made by detecting fetoplacental anasarca, pleural or pericardial effusion at the prenatal ultrasonography [2, 6, 21]. Decision of the operation time can be made depending on the gestation weeks and hemodynamic condition of the fetus. If fetal hidrops occurs, an emergency operation should be made. Operations can be made after early delivery or intrapartum by uteroplacental circulation support [21–23]. Teratomes can also cause extrinsic cardiac compression in infants but usually asymptomatic in adults.

The first successful resection of a pericardial teratoma was published by Beck in 1942 [17]. Teratomas are usually well encapsulated and have a single blood supply. Surgery is straightforward and successful when the tumor can be totally resected [6]. Operation is necessary in symptomatic cases. Pericardiocentesis or drainage of the cystic component of a teratoma are not curative options. Mature teratomas are relatively insensitive to both chemotherapy and RT. Immature malignant teratomas may benefit from partial excision and application of adjuvant chemotherapy includes vincristin, bleomycin, cisplatin and radiotherapy [12].

Hemangioma

Hemangiomas are common tumors but are rarely located at the pericardium. Only %2.8 of benign pericardial tumors are hemangiomas and usually arise from the visceral pericardium [24]. They are mostly a cavernous type and rarely cause symptoms. Atypical complaints occur in gigantic tumors [6]. Pericardial hemangiomas typically appear as a hyperechoic lesion at echocadiography. CT scans reveal pericardial masses with non-homogenous and irregular contrast enhancement [24]. Hemangiomas appear as intermediate T1-weighted signal intensity and high T2-weighted signal intensity at MRI [2]. Hemangiomas can be distinguished from angiosarcomas on imaging based on the presence of findings, including the presence of well-circumscribed tissue planes without invasion [18]. Radical resection of the tumor is recommended because of the possibility of hemorrhage and potential for recurrence [6, 18].

Paraganglioma

Paragangliomas arise from the paraganglion cells derived from neural crest and do not occur commonly in the chest. Although paragangliomas are neuroendocrine tumors and usually secrete catecolamines, pericardial paragangliomas are mostly inactive [2, 6]. Hormonally active tumors are frequently located elsewhere in the thorax [25]. While active tumors cause such symptoms as hypertension, headaches, tremors and palpitations due to elevated plasma catecolamines, nonactive tumors are usually silent and complaints occur only because of the development of compression on mediastinal structures [2]. Paragangliomas may be localized with echocardiography, they usually appear as circumscribed, heterogeneous masses with low attenuation on CT. They are vasculary lesions and enhance after contrast administration. Central necrosis is common and appears as low attenuation in the central area [6]. The characteristic MR imaging feature is hyper-intense signal with T2-weighted sequences [2]. A 24-hour urine test for metanephrine measurement shows the neuroendocrine activity of the tumor. Nuclear medicine imaging using iodine 131 or 123 metaiodobenzylguanidine can localize the hormonally active tumors [6].

Pericardial paragangliomas can be either benign or malignant. Irrespective of the presence of symptoms, resection indicated for all pericardial paragangliomas because both benign and malignant lesions can invade adjacent structures, usually coronary arteries [6, 18, 26]. Coronary angiography is required to determine coronary invasion. Cardiac transplantation is a choice if complete resection is not possible because of the coronary invasion [27].

Malignant Pericardial Tumors

Mesothelioma

Mesothelioma is the most common primary malignant tumor of the pericardium although they represent fewer than %1–2 of all malignant mesotheliomas [3, 18]. Reported prevalence was %0.0022 at autopsy series. There is a 2:1 male-female ratio [2]. Most of the patients were at the fifth to seventh decade of their lives at the time of the diagnosis. Sporadic cases were also established as benign cardiac mesotheliomas located at the atrioventricular node [6]. The relationship between asbestos exposure and pericardial mesothelioma has not been well established yet [2, 4, 26]. Mesotheliomas have been classified due to the predominant tissue of the lesion. Three variants exist; epithelial, fibrous (spindle cell) and biphasic (mixed) [2, 4]. Epithelial cell variant is the most common in pericardial mesotheliomas [2]. The fibrous type rarely occurs but CT may easily detect this variant. Gross morphology of pericardial mesotheliomas differs from a single mass and multicentric tumors to diffuse plaques involving each layer of the pericardium [4]. Symptoms are vague and lesions are silent since metastasis occurs [10]. Constrictive pericarditis, pericardial effusion and tamponade can also develop in patients. The lesion was detected in only %12 of the cases by echocardiography [6].

The tumor appears on both CT and MR images as a heterogeneously enhancing mass at either the parietal or the visceral layers of the pericardium. But reported sensitivity of the CT is low too (%44) [6]. Pericardiocentesis may yield a cytologic diagnosis [26]. The prognosis is extremely poor due to it's generally late presentation [6, 10]. The only treatment option is surgical approach but when the diagnosis was made, metastatic lesions were found in nearly %50 of the cases. Radical pericardiectomy should be performed because of the risk of recurrence [2, 10, 26]. Chemotherapy and radiotherapy have a limited effect on survival. Rapid clinical detoriation and death occurs 4 to 12 months after diagnosis, in inoperated cases [4, 10].

Sarcoma

Primary pericardial sarcomas are uncommon pathologies with a wide range of histologic appearances. All types of sarcomas have been reported as case reports in the heart and pericardium but the synovial sarcomas and agiosarcomas are the most common reported types [26]. Association with a characteristic chromosomal translocation $t(X; 18)$ has been described for synovial sarcomas [18]. Prognosis is poor like other malignant pericardial pathologies. Resection should be done in early stage cases. Even if lesions can be totally resected, recurrence often occurs and median survival was reported as 3–12 months [2]. Chemotherapy and radiation therapies may prolong survival [28].

Synovial sarcomas and angiosarcomas are higly vascularized tumors and heterogeneously enhance on the CT images. They can be misdiagnosed as pericarditis because pericardiocentesis commonly reveals a hemorrhagic effusion with no evidence of atypical cells. They can resemble mezothelioma at hystological analysis [2].

Liposarcomas are slow-growing tumors and have an invasive nature. At the time of the diagnosis complete resection can not be done because of the size and adjacent structure invasions. Pericardial liposarcomas appear as predominantly fatty, heterogeneous masses with areas of low-attenuation values on CT images [2].

Lymphoma

Primary pericardial lymphoma is an extranodal lymphoma and usually be diffuse large B cell type. They appear as low attenuation with heterogeneous enhancement mass on CT images. Pericardial thickening, effusion, and a mass with heterogeneous postcontrast delayed enhancement pattern can be seen on MR images. The standard therapy is anthracycline-based chemotherapy but the prognosis is generally poor [2, 18].

Secondary Pericardial Tumors

The most common pericardial masses are secondary pericardial tumors. They are metastatic lesions therefore careful evaluation for underlying other malignancies should be done if a mass is seen in pericardium. Although metastatic involvement of pericardium was reported highly in autopsy series the pericardial effusion is the most common seen pericardial pathology in these patients [2, 5, 18]. Lung and breast carcionams are the most common primary malignancies. Melanoma, lymphoma, and leukemia are other common underlying pathologies [18, 29]. Imaging findings include presence of effusion, irregular thickening of the pericardium or nodularity, and distinct pericardial masses. Cytologic analysis is oftenly used rather than tissue biopsies for diagnosis. But the morphological similarity between the reactive mesothelial hyperplasia and carcinomas lead to a misdiagnossis. Therefore usage of the immunohistochemical studies are recommended [10, 18]. Secondary pericardial tumors have a short life expectancy (median 2–4 months) however prognosis may be better in certain subsets of patients, such as those without malignant cells in the pericardium. Relieving of the cardiac compression is the first step theraphy. Systemic antineoplastic treatment for primary malignancies is recommended. Intrapericardial instilllation of cisplatin was found effective in non-small cell lung cancer and thiotepa in breast cancer metastases [10].

Self-study

1. Which one is the most common radiological finding in pericardial tumors
   (a) Pericadial effusion
   (b) diffuse pericardial thickening
   (c) Nodular pericardial thickening
2. Which one is the most recommended technique for biopsy procedures because of the higher rate of diagnosis.
   (a) Direct chest X-ray guided procedures
   (b) Ultrasonography or echocardiography guided procedures
   (c) CT guided procedures
   (d) MRI guided procedures
   (e) Pericardioscopic procedures
3. In symptomatic pericardial cysts which one is the first chosen treatment modality?
   (a) Aspiration
   (b) Aspiration and sclorotic material instillation
   (c) Surgical resection
4. Which one can causes fetal or neonatal death?
   (a) Pericardial lipoma
   (b) Pericardial hemangioma
   (c) Teratoma
5. Which one is correct for pericardial mesotheliomas
   (a) Pericardial mesotheliomas appear as well defined, non-enhancing, homogeneous fluid-attenuation lesions that contain no internal septa.
   (b) They are neuroendocrine tumors.
   (c) Mesotheliomas are the most common primary malignant tumors of the pericardium.
   (d) The standard therapy is anthracycline-based chemotherapy but the prognosis is generally poor.

Answers

1. Which one is the the most common radiological finding in pericardial tumors
   (a) Pericadial effusion **–CORRECT.**
   (b) diffuse pericardial thickening
   (c) Nodular pericardial thickening
2. Which one is the most recommended technique for biopsy procedures because of the higher rate of diagnosis.
   (a) Direct chest X-ray guided procedures.
   (b) Ultrasnonography or echocardiography guided procedures.
   (c) CT guided procedures.
   (d) MRI guided procedures.
   (e) Pericardioscopic procedures **–CORRECT.**
3. In symptomatic pericardial cysts which one is the first chosen treatment modality?
   (a) Aspiration.
   (b) Aspiration and sclorotic material instillation. **–CORRECT.**
   (c) Surgical resection.
4. Which one can causes fetal or neonatal death?
   (a) Pericardial lipoma.
   (b) Pericardial hemangioma.
   (c) Teratoma**–CORRECT.**
5. Which one is correct fot pericardial mesotheliomas
   (a) Pericardial mesotheliomas appear as well defined, non-enhancing, homogeneous fluid-attenuation lesions that contain no internal septa.
   (b) They are neuroendocrine tumors.
   (c) Mesotheliomas are the most common primary malignant tumors of the pericardium-**CORRECT.**
   (d) The standard therapy is anthracycline-based chemotherapy but the prognosis is generally poor.

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Intraoperative Accidents and Postoperative Complications in the Surgery of the Pericardium

Mehmet Aksüt, Özge Altaş, and Kaan Kırali

Abbreviations

VATS	Video Assisted Thoracoscopic Surgery
ECG	Electrocardiography
CVP	Central Venous Pressure
TEE	Trans Esophageal Echocardiography
CPB	Cardio Pulmonary Bypass
CT	Computer Tomography
IABP	Intra Aortic Balloon Pump
NHYA	New York Heart Association
COPD	Chronic Obstructive Pulmonary Disease
GIS	Gastro Intestinal System
MI	Myocard Infarction
ECMO	Extra Corporeal Membrane Oxygenation

Key Points

- Pericardial surgery is performed in effusive, constrictive and neoplastic pericardial pathologies.
- Additional comorbidities affect long-term results after pericardial surgery.
- Pericardiectomy is the most commonly performed surgical procedure in pericardial diseases.
- Recurrence rate is high after palliative techniques on the other hand complications is more frequent in total corrections

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Introduction

Pericardium is a passive but protective structure that surrounds the heart and large vessels. There are two layers, visceral and parietal. The visceral pericardium folds on itself at the origin of the great vessels and forms the inner layer of the parietal pericardium. The outer layer of parietal pericardium consists of fibrous connective tissue. The elasticity of the pericardial tissue is limited and there is a lubricated serous liquid of about 20–50 ml to reduce the mechanical friction of the heart between the two layers. The pericardium separates the heart from the other adjacent structures as well as creating a mechanical barrier by surrounding the heart. Usually there are pericardial thickening, constrictive pathology and pericardial effusion in pericardial diseases and result in cardiac diastolic dysfunction. Clinical presentation is usually the same, but treatment depends on etiology and disease severity.

Pericardial diseases can be divided into constrictive, non-constrictive and neoplastic

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pathologies from the surgical standpoint [1]. Non-constrictive diseases of pericardium, disrupting hemodynamics by causing excessive fluid accumulation in the pericardial space in the acute, sub-acute or chronic period; bleeding (penetrating injuries, catheter-based procedures, post-cardiac surgery), inflammation and infection. Constrictive diseases are constrictive pericarditis, inflammation, infection, cardiac surgery, mediastinal radiation and idiopathic causes resulting in the pericardium losing elasticity [2]. The tumors are another pericardial disease which requiring surgery. The most common pathologies in this group are benign tumors and cystic diseases. In general, these are clinically relevant. On the other hand, pericardial malignancies are rare and clinically noisy. Constrictive pathophysiological findings may also develop in primary and metastatic neoplasms of the pericardium [3].

The methods used in pericardial surgery can be grouped under three main headings: mediastinal exploration, pericardial window opening (subxifoid or transpleural approaches) and pericardiectomy [1].

Mediastinal exploration has an important place in the surgical management of pericardial diseases. Catheter-based cardiac procedures, which are increasingly used today, can cause cardiac injury. If the injury is simple and can be recognized early, the accumulated pericardial fluid may be drained by percutaneous interventions without the need for surgical intervention. If uncontrolled bleeding or existing cardiac pathology requires surgical intervention, emergency mediastinal exploration is indicated. If pericardial fluid accumulation develops rapidly after cardiac surgery, mediastinal re-exploration should be preferred before pericardiocentesis. Both the detection and repair of the source of the bleeding will be easier. If the character or location of pericardial effusion is not suitable for percutaneous drainage, surgical drainage should be performed. Mediastinal exploration also allows for biopsy from pericardial tissue.

Another approach used in pericardial diseases is pericardial window procedure. In this technique, drainage of the pericardial fluid can be made by both subxiphoid approach directly and transpleural way indirectly. Although transperitoneal approach also has been reported as a method for pericardial fluid drainage, most of the surgeons prefer either subxiphoid or transpleural path [1]. Transpleural approach is mainly used for malignant or recurrent effusions and it needs one-lung ventilation. Transpleural approach can be operated via a small anterior thoracotomy or video assisted thoracoscopy. Subxiphoid approach is used generally for effusions collected following cardiac surgery or infectious pathologies. One-lung ventilation is not a necessity for this strategy and simple local anesthesia is adequate most of the time [4].

Although pericardiectomy is the gold standard treatment modality of chronic constrictive pericarditis, it is recommended that it should be performed by experienced surgeons [5]. Intraoperative accident, early and late reported complication rates are still high. It has been reported that if constrictive pericarditis is diagnosed before the onset of calcification, severe constriction and myocardial atrophy, it is easier to operate with relatively low recurrence rates and better symptomatic recovery. Pericardiectomy can be practised using median sternotomy, left anterolateral thoracotomy, bilateral thoracotomy and VATS (video assisted thoracoscopy) with or without cardiopulmonary bypass.

According to the amount of pericardium resected, total, radical or partial pericardiectomy techniques have been described [1]. Total pericardiectomy was described by Chowdhury et al. (2006) as removal of the whole pericardium overlying the heart and great vessels except for the pericardium posterior to the left atrium in the oblique sinuses [2]. Radical pericardiectomy has ben used to describe removal of the anterior pericardium (phrenic nerve to phrenic nerve), the diaphragmatic pericardium and pericardium posterior to the left phrenic nerve. Partial (sub-total or anterior) pericardiectomy is defined as removing only the anterior portion of pericardium from the right to left phrenic nerve [1, 6]. Still there is not any consensus about the amount of pericardium that should be resected [1, 2, 6, 7]. Even though Nataf et al.

(1993) reported anterior pericardiectomy as satisfactory treatment with low recurrence rates, comprehensive pericardiectomy series revealed that anterior pericardiectomy is associated with high recurrence rates. Because of that, radical pericardiectomy was recommended as standard treatment [1, 7, 8]. Lachman et al. noticed that 58% of whole pericardium, 26% of the pericardium covering the left ventricle can be reached with median sternotomy [9]. With left anterolateral thoracotomy, 37% of the pericardium of left ventricle and 63% of the whole pericardium can be reached [7].

Following the general anesthesia, proper positioning according to surgical approach is given. The patient is monitorised maximally; ECG, CVP, continuous invasive arterial pressure, pulmonary arterial pressure, saturation etc. Defibrillation pads and TEE probe are placed. Cardiopulmonary bypass machine and a perfusionist are kept ready in operating room. Median sternotomy is the preferred approach due to better exposure because gives wide access to the pericardium. This method also simplifies bleeding control and cannulation if CPB necessary.

To avoid sternal infection in patients with pericarditis caused by infective etiologies, left anterolateral thoracotomy can be performed [10]. Left anterolateral thoracotomy can also be used due to re-sternotomy risk in patients with sternotomy history. With left anterior thoracotomy, posterolateral pericardium resection can be accomplished without the need of CPB but in this method, it is very hard and limited to reach right side of the heart and diaphragmatic surfaces. If additional exposure is necessary anterolateral incision can be extended to a bilateral thoracotomy. Axillary or femoral access sites should be kept open because urgent cardiopulmonary bypass may be required.

In case of concomittant cardiac surgery requirement, severe fibrosis, massive calcification or partial pericardiectomy history, it may be safer to operate with CPB due to the risk of major cardiac injury and catastrophic bleeding [11].

Problems Possible to Encounter During Surgery

Injuries and Massive Bleeding

Pericardial diseases usually goes with inflammation and might affect the membranes around. As a result of this, adhesion of pericardium to surrounding structures can be seen. It is hard to notice this before surgery. Similar with the pre-operative assessment of re-sternotomy patients with thorax CT, distance between the sternum and the heart is important. Patients with history of mediastinal radiation or cardiac surgery, undesired major injuries or bleeding may occur due to adhesions between sternum, heart and great vessels. That's why CPB should be kept ready before the onset of the surgery. If thoracotomy is preferred, parenchymal lung injuries may occur. Decompression of the related lung must be made.

After thoracotomy or sternotomy, pericardium is evaluated. Pericardium is inspected and palpated carefully to detect the calcific areas of the pericardium and their contiguities with great vessels, epicardial cardiac vessels, phrenic nerves. After the examination of pericardium, it is determined where to start the pericardiotomy. Between the visceral and parietal parts of the pericardium, a safe cleavage is created. In some constrictive pericarditis patients, deep penetration of calcification into the myocardium can be observed. Especially in those cases, resection of the calcifications under CPB is safer due to low ventricle pressures. With left anterolateral thoracotomy, right atrioventricular junction, right atrium, pericardium covering the vena cavas and diaphragmatic surfaces are limited to reach. It should not be insisted on resecting calcifications and adhesions totally. Otherwise major cardiac injuries may happen. In this situation, instead of total resection of calcified pericardium, WAFFLE procedure can be an option [12]. In addition to this, epicardial vascular injuries might take place. Consequently perioperative myocardial infarction and malignant arrhythmias may take place.

With left thoracotomy, it is possible to resect pericardium on both sides of left phrenic nevre. In case of thickening and calcification of pericardium, phrenic nerve might not be seen well. To detect the exact location of phrenic nerve, proximal temporary pacemaker stimulation can be made [13]. To avoid phrenic nerve injury, 1–1.5 cm of tissue is left around phrenic nerve.

Subxiphoid approach is often preferred in post-cardiotomy patients but may cause chamber rupture due to limited exposure. At the same time due to adhesions and fibrin networks formed after surgery, loculated pericardial fluids may not be drained adequately.

Pulmonary Congestion

Sequence of decortication is significant. Decortication is made from outflow sides to inflow sides of the heart. Leaving great arteries with contsriction, if started with ventricular decortication subendocardial ischemia and hemodynamic instability may happen due to increased ventricular pressure. Relieving the constriction of right ventricle before left ventricle may cause the pooling of blood within pulmonary circulation and lung edema. That's why pericardial resection is started in order of aorta, left ventricle, pulmonary artery, right ventricle, left atrium, pulmonary veins, diaphragmatic surfaces, right atrium and vena cavas.

Hemodynamic Instability

Another problem encountered frequently during pericardiectomy is hemodynamic instability. During complete pericardiectomy with median sternotomy, manipulation of the heart to remove pericardium posterior to the left phrenic nerve may cause blood pressure to fall. These manipulations may cause malignant arrhythmias, catastrophic injuries and hemodynamic instability. Weighing the risks of CPB, if the purpose is complete pericardiectomy, operation can be made safely under CPB. Left anterolateral thoracotomy is another option to reach the side mentioned above. Electrocautery usage in pathologies with deep myocardial invasion may cause arrhythmias. In some centers, harmonic cautery or cavitational ultrasonic aspiration systems are used for deeper dissection [6].

After the pericardiectomy, following the relieve of constriction over heart, biventricular filling pressures increase suddenly. Myocardium might not adapt this pressure increase with same speed and acute heart failure comes off. That's why in patients with low cardiac function, intraoperative inotropic support initiation will be beneficial. If necessary, IABP can also be used.

Post Operative Complications

Despite the developments of surgical techniques and intensive care conditions; the complication rate after pericardial surgery is still high.

Gopaldas et al. (2013) reported that only 62% of 13593 cases who had undergone pericardial surgery were discharged [14]. Even in the most experienced centers, the 30-day mortality rate is higher than other cardiac surgery procedures and ranges from 5.2 to 13% [5, 6, 15, 16]. Many mortality predictors have been found. The most effective ones are age, gender, NYHA class, etiology, poor ventricular function, pulmonary hypertension, concomitant cardiac pathologies, hepatic and renal dysfunctions, COPD, advanced disease grade, hyponatremia, radiotherapy or history of cardiac surgery [1, 5, 15, 16].

Patients undergoing pericardiectomy require close hemodynamic monitoring, rhythm monitoring, inotropic support, diuretic therapy and cardiac output optimization in postoperative intensive care follow-up [6]. In the early postoperative period GIS bleeding, pulmonary edema, arrhythmia, pericardial tamponade requiring re-operation, peri-operative MI, renal failure, diaphragm paralysis and consequent prolonged intubation, cardiopulmonary insufficiency, pneumonia, empyema, wound site infection, sepsis and multi-organ failure can be seen [5, 14, 15, 16, 17].

Patients needing diuretic therapy in the pre-operative period and who have advanced congestive symptoms, long-term survival may not be achieved even if successful pericardiectomy is performed. Low cardiac output in the early period can be treated with fluid restriction, inotropic support, high dose digitalization and IABP support [5]. In some series, up to 12% of the patients who underwent pericardiectomy with chronic constrictive pericarditis needed ECMO support [16].

A consensus on the amount of pericardium to be resected in constrictive pericarditis has not yet been reached. Some publications insistently suggest radical pericardiectomy but partial pericardiectomy is still preferred by many clinics because it can be applied easily, CPB support is usually not required and it has low risk of phrenic nerve and major cardiac injury [6, 7, 15, 18–20]. Publications defending radical pericardiectomy; postoperative recovery was attributed to inadequate surgery. The publications defending radical pericardiectomy have attributed poor postoperative healing to inadequate surgery. The publications defending partial pericardiectomy was attributed poor postoperative healing to myocardial atrophy and concomitant pathologies [6, 7, 20]. Myocardial atrophy was seen at a rate of 25% in the post-mortem analysis of constrictive pericarditis and was the most important factor predicting mortality-morbidity [5, 21]. Partial pericardiectomy should include two phrenic nerves and diaphragmatic surface. In patients with symptoms of right heart failure, removal of the construction around the vena cava provides a faster clinical improvement and is important in the absence of recurrent symptoms in the long term.

Tricuspid regurgitation is frequently seen in patients with constrictive pericarditis. The degree of tricuspid regurgitation may increase after surgery. Therefore, valve functions should be evaluated by intraoperative TEE during pericardiectomy operation. In the evaluation, pre-operative tricuspid annulus diameter may not be a good indicator because, after decortication, the tricuspid annulus dilates with the right ventricle and the tricuspid annulus diameter increases in the post-operative period and the degree of tricuspid regurgitation may increase. For this reason, tricuspid valve intervention should be considered even in moderate tricuspid regurgitation to avoid early or late right heart failure [22].

In purulent pericardial effusions due to infectious etiologies, the transpleural approach may lead to infection in the pleural cavity and empyema. If empyema develops, mortality increases and is reported up to 8% in some publications [5].

Some uncommon complications after pericardial surgery have been reported in case reports. Alimi et al. (2015) reported in the case report; a patient who underwent left intrapericardial pneumonectomy due to lung cancer, cardiac herniation was seen in the postoperative early period after pericardial resection. Although cardiac herniation is usually seen in the first 24 hours, late period cases are also found in the literature. Although it is a fatal complication, it can be prevented. It is recommended to patch the pericardial defect, especially in cases accompanied by pneumonectomy [23]. Iatrogenic coronary artery fistula between coronary arteries and cardiac chamber or vascular structures have been reported. Unzue et al. (2017) showed a large arteriovenous fistula between coronary sinus and circumflex coronary artery in a patient who presented with heart failure, angina and dyspnea 14 years after pericardiectomy operation. The fistula was successfully closed by percutaneous route [24].

Conclusion

Developing technology provides many new possibilities in cardiothoracic surgery but mortality and morbidity rates are still high in pericardial surgery. This may be due to the lack of consensus in the early diagnosis and treatment of pericardial diseases. The success of the treatment depends on the etiology of the pericardial pathology, the comorbid factors of the patients and the experience of the surgeon. During the operation, vital structure injuries and hemodynamic

disturbances may develop. Even if the operation is successful, many problems can be encountered in the early and late postoperative period. Therefore, medical treatment support and follow-up of the patients are also important.

Self-study

1. Which of the followings are true?

In pericardial effusive diseases,

I. Diastolic cardiac functions are less affected than systolic cardiac functions.
II. Subxiphoidal and trans-pleural drainages are one of the most frequently preferred approaches.
III. If the etiology is stem from early period of post cardiac surgery and infection, subxiphoidal drainage should be preferred.

(a) I, (b) I, II, (c) II, III, (d) I, II, III, (e) None

2. Which one of the following is true?

I. Pericardiectomy is the gold standard treatment method in chronic constrictive pericarditis.
II. In chronic constrictive pericarditis, anterior pericardiectomy is generally sufficient to achieve a good clinical outcome without recurrence and complication rate is less than other pericardiectomy techniques.
III. Lachman et al. reported that median sternotomy is a more advantageous technique than left anterolateral thoracotomy in order to access pericardium which covers the left ventricle.

(a) I, III, (b) None, (c) I, (d) I, II, (e) I, II, III

3. Which one of the following is false?

I. In cases of constrictive pericarditis due to infectious etiology, left anterolateral thoracotomy is the most preferred surgical approach for pericardiectomy.
II. In pericardiectomy, median sternotomy is frequently preferred to avoid the surgical complications and to cope with the potential complications more easily.
III. Posterolateral pericardium resection can generally be performed with left anterior thoracotomy without the need for performing cardiopulmonary bypass.
IV. When there is a need for concomitant cardiac surgery intervention, performing pericardiectomy with median sternotomy approach and under cardiopulmonary bypass is safer in the presence of extreme adhesion and massive calcification.

(a) I, (b) II, (c) II, III, (d) I, IV, (e) None

4. Which of the followings are true?

I. When performing pericardiectomy, no matter which approach is chosen, it is important to examine pericardium carefully.
II. In the presence of massive calcification which goes beyond myocardium, pericardiectomy should be performed under cardiopulmonary bypass.
III. When performing pericardiectomy, there should be a safety distance at about 1–1.5 cm in order to avoid phrenic nerve nerve injuries.
IV. When performing pericardial resection, at first, aorta and left ventricle should be released, and then pulmonary artery, right ventricle, left atrium, pulmonary veins, diaphragmatic surfaces, right atrium and vena cavas should be released, respectively.

(a) I, III, (b) I, II, IV, (c) I, II, III, IV, (d) None, (e) IV

Answers

(1) C
(2) C
(3) E
(4) C

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Anatomy and Embryology of the Diaphragm

Wilson King and Benjamin Wei

Key Points

- The diaphragm is a large musculotendinous organ that separates the thoracic and abdominal cavities. Its major blood supply is from the inferior phrenic arteries, and its major innervation is from the phrenic nerve.
- Three large diaphragmatic apertures exist for the passage of the inferior vena cava, esophagus, and aorta.
- Special attention must be given when making an incision in the diaphragm as to not injure the phrenic nerve.
- The septum transversum becomes the central tendon of the diaphragm, and the pleuroperitoneal membranes becomes much of the musculature of the diaphragm.
- Congenital diaphragmatic hernias occur due to defective fusion of the pleuroperitoneal membranes with the septum transversum.

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Introduction

The diaphragm is a large musculotendinous organ that provides the largest component to the work of breathing and divides the body into thoracic and abdominal cavities. It has a rich bloody supply and a long coursing innervation. An understanding of the anatomy and embryology of the diaphragm is a foundational step in understanding physiology, pathophysiology, and related surgical interventions.

Anatomy

The diaphragm is a large musculotendinous organ that separates the abdominal and thoracic cavities. It is made up of a non-muscular central tendon and three groups of musculature peripherally. The central tendon is composed of a right, left, and middle leaflet with the right leaflet representing the largest portion. Although named *central*, the tendon is more anterior and superior than central. The three muscular groups are the pars costalis, pars lumbalis, and pars sternalis. The pars costalis originates from the inner surface of the lower six ribs and insert onto the central tendon. The pars lumbalis is the strongest part and located by the lumbar spine forming the right and left crura. The right crus, originating from L1–L3, is larger than the left crura, originating from L1–L2. Most often, the

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right crus splits to form the esophageal hiatus (Fig. 1).

The diaphragm has three large openings for passage of the inferior vena cava (IVC), esophagus, and aorta (Fig. 2). The IVC hiatus occurs in the central tendon at the level of T8. The right phrenic nerve and some lymph vessels also run through this opening. Interestingly, during inspiration, the diaphragm will contract thus stretching this opening causing increased venous flow

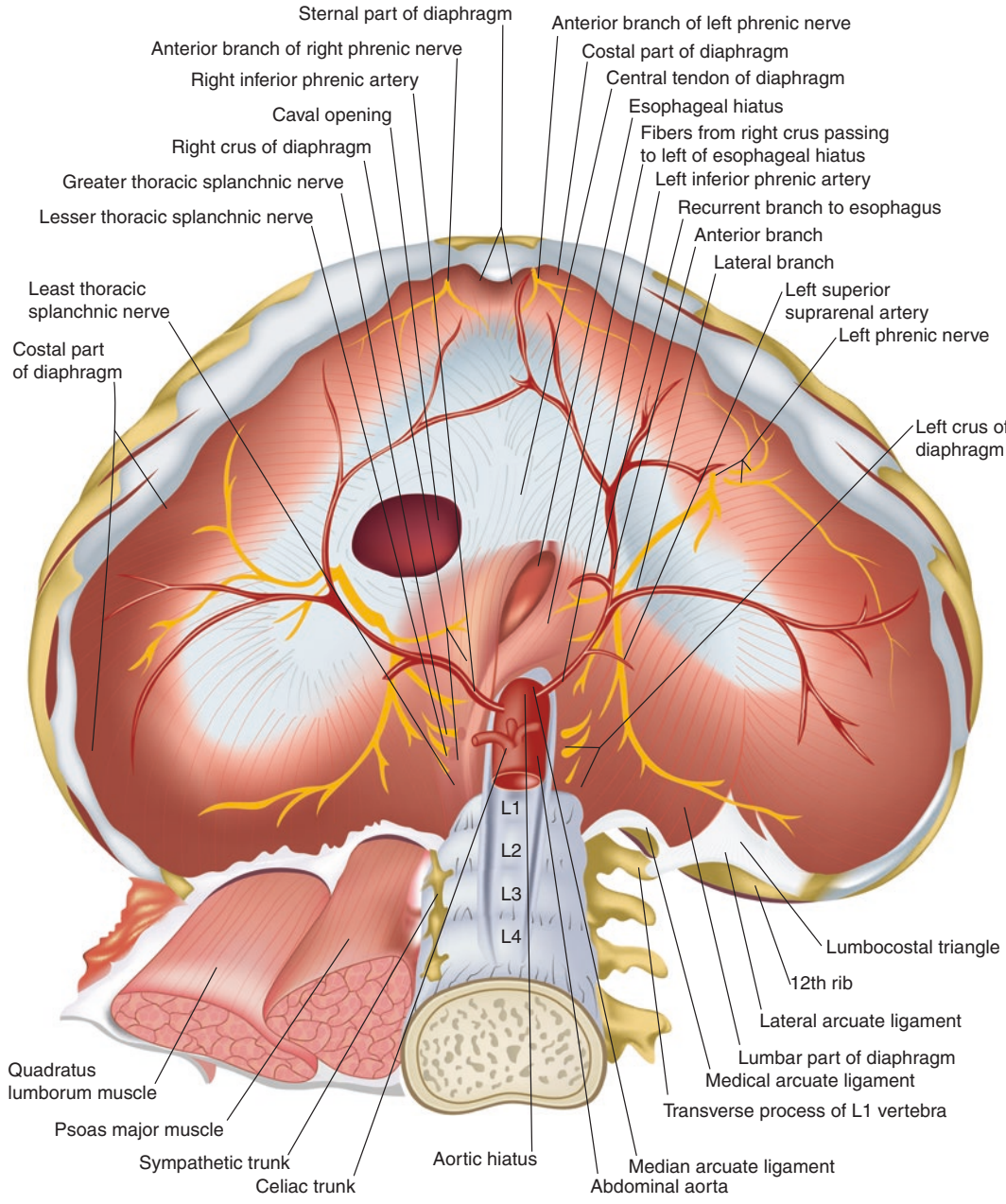

Fig. 1 Abomdinal view of the diaphragm. Its rich bloody supply, innervation, and musculotendinous components are shown, as well its relation to the quadratus lumobrum and psoas muscle. The diaphragm apertures are also nicely visualized. from NetterImages

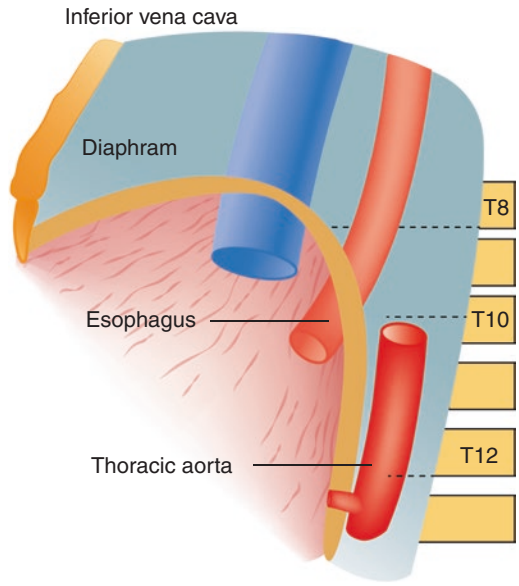

Fig. 2 Diaphragmatic apertures and corresponding vertebral levels. from https://www.passthemrcs.co.uk/stations/22/questions/379

up the thorax. The esophageal hiatus occurs slightly left of midline at the level of T10. This opening also provides passage to the vagus nerve, sympathetic trunk, and lymphatics. The final large opening is the aortic hiatus between the crura at the level of T12. The azygos vein, thoracic duct, and lymphatic vessels also run through this opening.

Blood Supply

The major blood supply to the diaphragm is from the paired inferior phrenic arteries arising from direct branches of the abdominal aorta. They bifurcate on the diaphragm posteriorly with branches coursing along the edges of the central tendon (Fig. 3). The branches anastomose with intercostal arteries and pericardiophrenic arteries. The internal mammary artery also provides arterial branches to the diaphragm

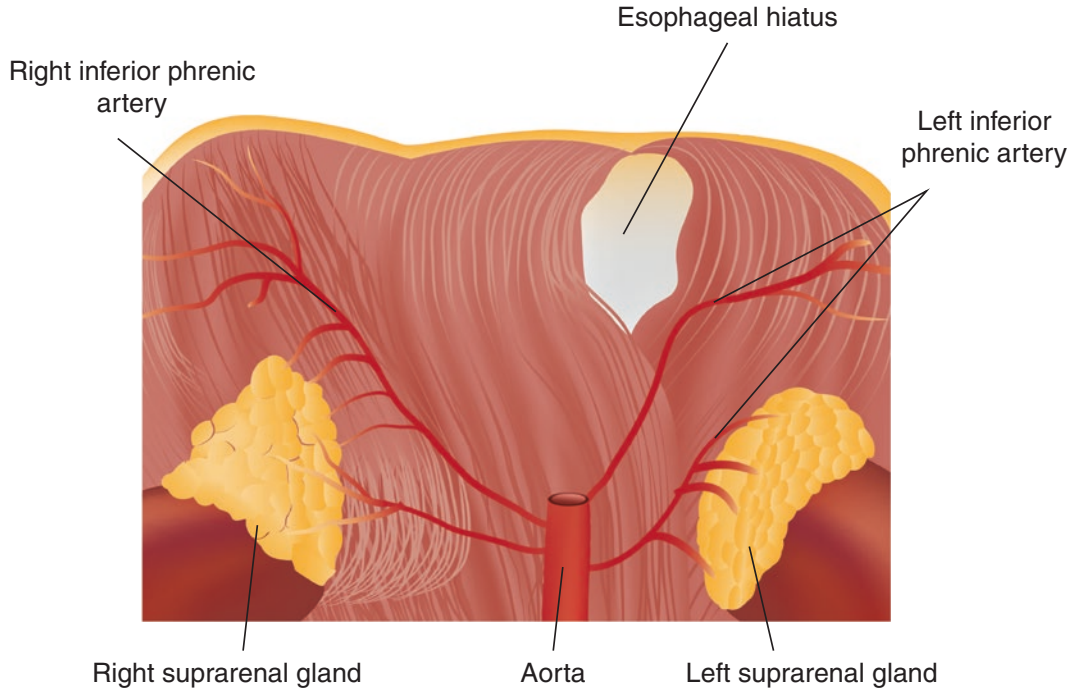

Fig. 3 Inferior phrenic arteries branching from the abdominal aorta. (Modified from Anderson JE: Grant's atlas of anatomy, 8th ed. Baltimore, Williams & Wilkins, 1983, Fig. 2-117A.)

superiorly. The right and left phrenic veins provide most of the venous drainage and drain into the IVC.

Innervation

The phrenic nerve, originating from C3–C5, provides both sensory and motor innervation to the diaphragm. After C3–C5 nerves join to make the right phrenic nerve, it proceeds inferiorly just anterior to the anterior scalene. It then courses behind the innominate vein and enters the thorax anterior to the subclavian artery. It continues inferiorly by running alongside the pericardium and anterior to the right lung hilum. It enters into the diaphragm just lateral to the IVC hiatus where it branches. The left phrenic nerve descends similarly by running anteriorly to the anterior scalene and posterior to the innominate vein. It then proceeds inferiorly by running alongside the pericardium. It finally enters the diaphragm just lateral to the left border of the heart. Both left and right phrenic nerves divides into anterolateral, posterolateral, sternal, and crural branches (Fig. 4). Notably, the outer rim of the diaphragm has some innervation from thoracic spinal nerves.

Surgical Considerations

The main consideration when operating near the diaphragm or in the chest is to avoid injury to the phrenic nerve. Intimate knowledge of the course of the phrenic nerve is needed so that it can be avoided during thoracic procedures. Even posterior neck dissections pose a risk to phrenic

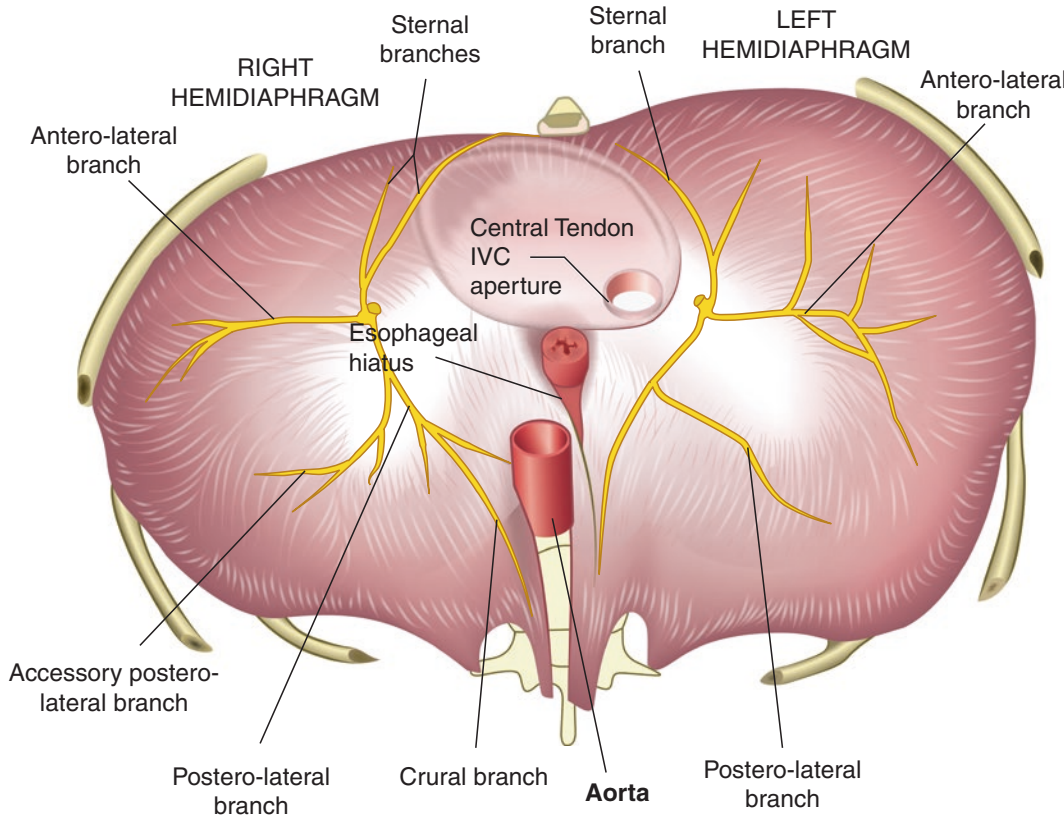

Fig. 4 Innervation of the diaphragm, superior view. The phrenic nerve gives rise to four branches, the anterolateral, posterolateral, crural, and sternal branches. From Pearson's thoracic and esophageal surgery

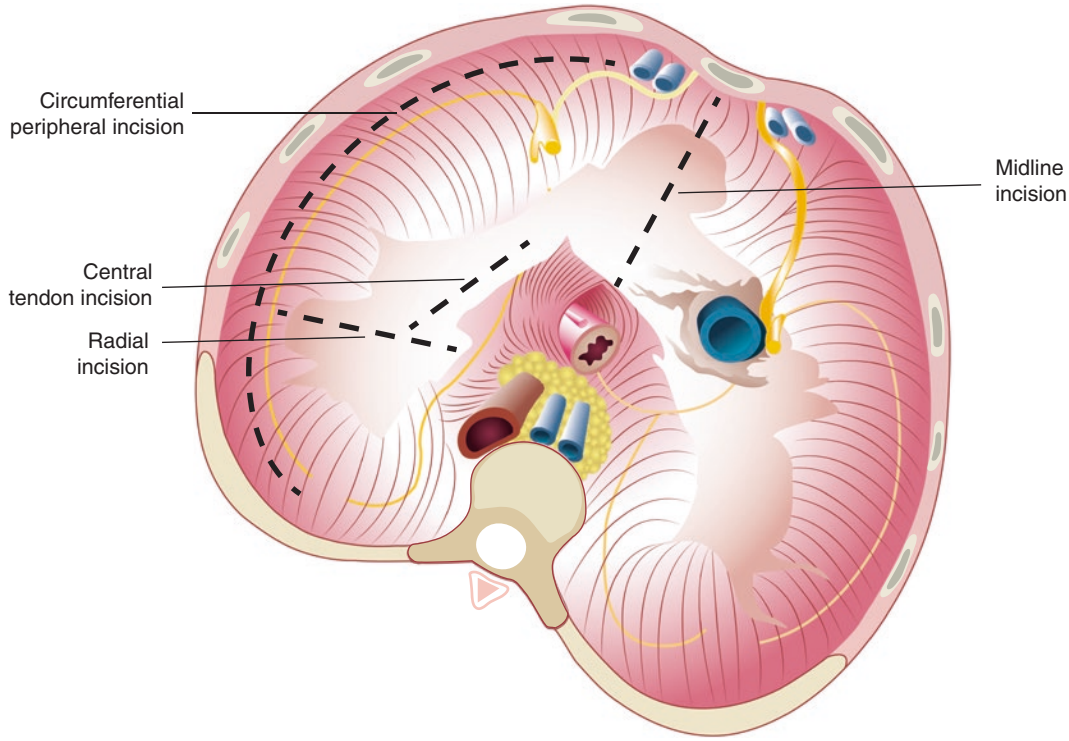

Fig. 5 Surgical incisions in the diaphragm. Shown are the different types of surgical incisions made in the diaphragm in order to avoid injury to the phrenic nerve. From Miash May, The Diaphragm

nerve injuries. If making a direct incision in the diaphragm, circumferential incisions near the periphery are almost always safe in avoiding nerve injury. Radial incisions can be used but need to be oriented as to only transect distal branches (Fig. 5).

Embryology

The formation of the diaphragm in the developing embryo is important in separating the thoracic and abdominal cavities. The diaphragm is made up of four different embryologic structures: the septum transversum, paired pleuroperitoneal membranes, body wall mesoderm, and esophageal mesoderm. However, understanding the embryology of the diaphragm begins with understanding some basics about the partitioning of the intraembryonic coelom into thoracic and abdominal cavities. The previously mentioned embryologic structures of the diaphragm will be bolded for clarity.

Creation of Thoracic and Abdominal Body Cavities

In week four of development, the embryo does not have defined thoracic and abdominal cavities (Fig. 6). However, the intraembryonic coelom exists, which lies caudal to the *septum transversum*, and begins to form a horseshoe around the cranial end of the embryo. During subsequent body folding, the intraembryonic coelom is repositioned and forms the pericardioperitoneal canals (sometimes referred to as pleuroperitoneal canals), a cranial pericardial cavity and a caudal peritoneal cavity. All of this body folding moves the *septum transversum* into a position that partially divides the intraembryonic coelom into a thoracic and abdominal orientation

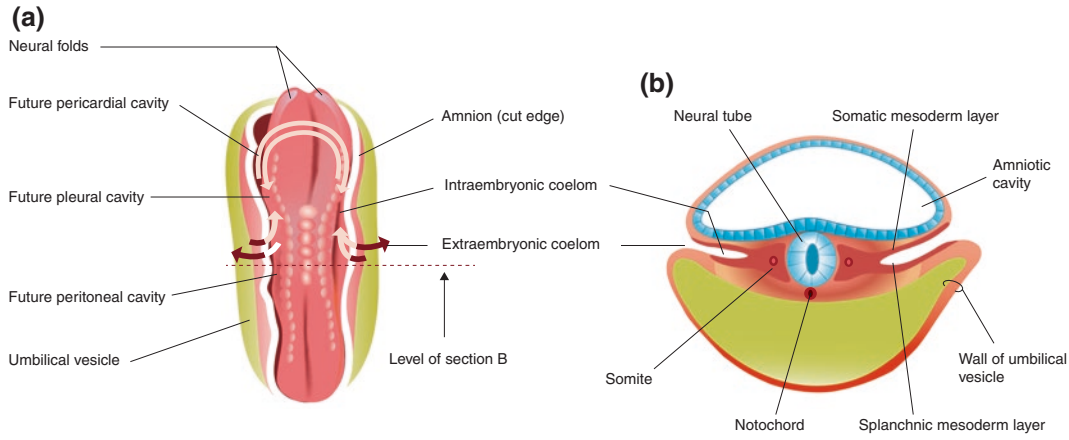

Fig. 6 The developing embryo before existence of defined abdominal and thoracic cavities. The intraembryonic coelom can be seen with surrounding origins of future body cavities. from http://embryocentral.blogspot.com/2015/01/development-of-body-cavities.html

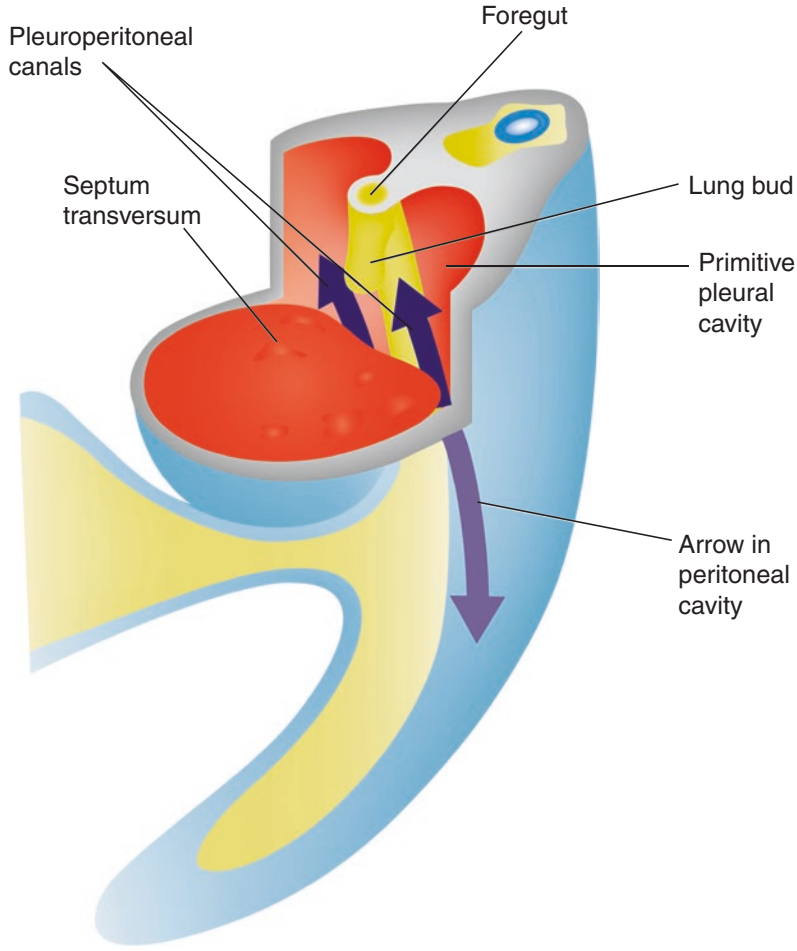

Fig. 7 Septum transversum partially dividing the intraembryonic coelom. Folding and growth of the embryo results in the pericardioperitoneal canals orientation dorsal to the septum transversum

with the pericardioperitoneal canals lying dorsal to the *septum transversum* (Fig. 7). Starting in week 5, paired *pleuroperitoneal membranes* form and begin moving ventrally to close the pericardioperitoneal canal. By the end of week 7, the growing *pleuroperitoneal membranes* completely fuse with the *septum transversum* thereby completing the division of the intraembryonic coelom into thoracic and abdominal portions [2] (Fig. 8). It is important to note that the left pericardioperitoneal canal is larger and closes more slowly than the right, which is important in understanding congenital diaphragmatic hernias.

Embryological Origins of the Diaphragm

The *septum transversum* becomes the central tendon of the diaphragm, while the *pleuroperitoneal membranes* becomes much of the musculature of the diaphragm. The left and right crura, however, are formed from *esophageal mesoderm* at the level of L1–L3. The last embryologic component of the diaphragm that has not been mentioned is the *body wall mesoderm*. It grows to form parts of the outer musculature of the diaphragm.

During growth of the embryo, spinal nerves from C3–C5 forms the phrenic nerve and migrate caudally with differentiating myoblasts in the *septum transversum*. These myoblasts move into the *pleuroperitoneal membranes* bringing the phrenic nerve with them and provide the diaphragm its phrenic nerve innervation. The outer rim of diaphragm musculature, derived from the *body wall mesoderm*, is not innervated by the phrenic nerve. This is because myoblasts from nearby somites migrated with the body wall mesoderm thereby providing its thoracic spinal nerve innervation.

Clinical Correlation: Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernias result when abdominal organs herniate through the diaphragm and bulge into the pleural cavity. If the bulge occupies enough space, the developing lungs are compromised resulting in lung hypoplasia (Fig. 9). The herniation occurs due to defective fusion of the pleuroperitoneal membrane with the septum transversum, although other theories exist [4]. Approximately 80% of all diaphragmatic hernias occur on the left side and this is thought to be due to slower closure of the left pericardioperitoneal canal secondary to its larger size [2]. These left sided

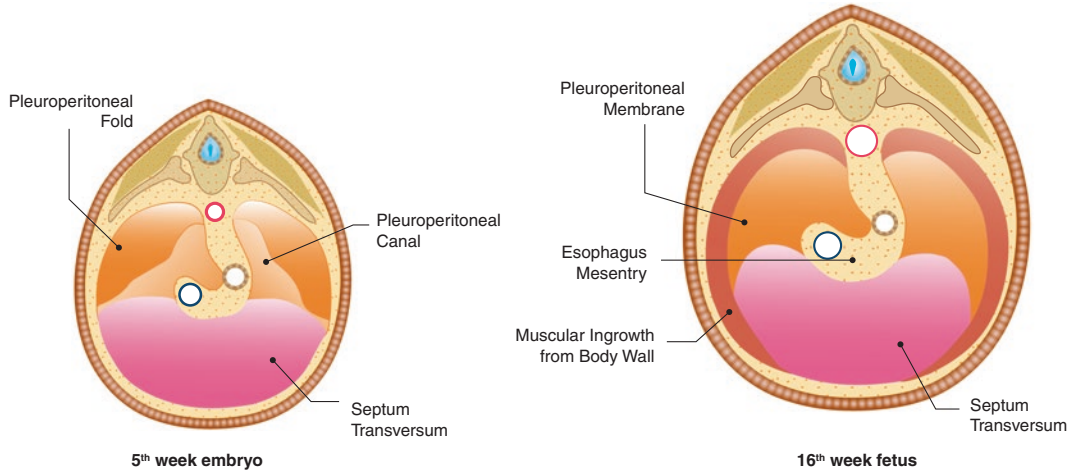

Fig. 8 Pleuroperitoneal membranes begin closing the pericardioperitoneal canal (pleuroperitoneal canal). from https://www.researchgate.net/figure/Embryogenesis-of-the-diaphragm-From-Lima-M-Ruggeri-G-2015-Difetti-Diaframmatici-In_fig1_305403881

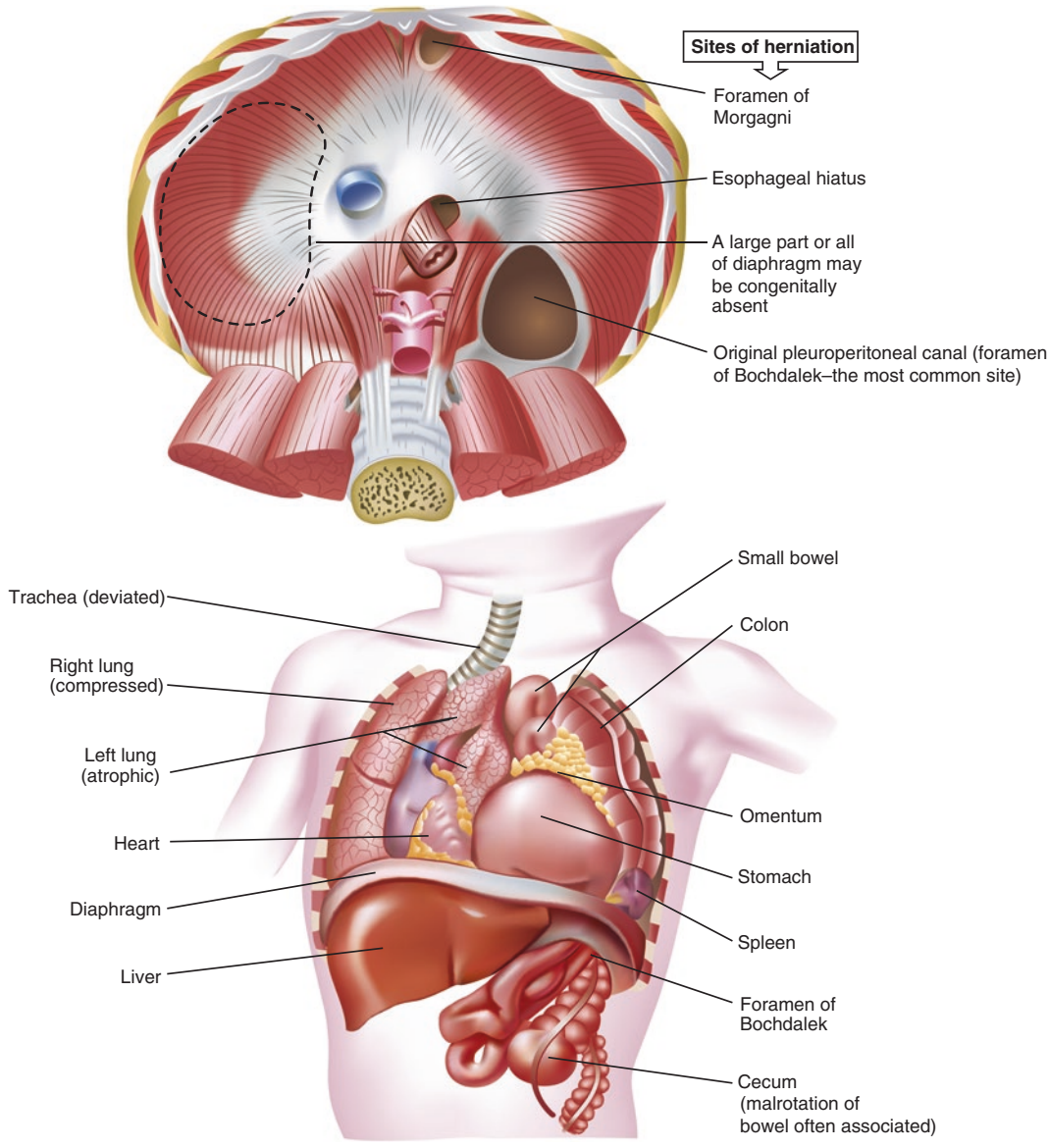

Fig. 9 Congenital diaphragmatic hernia causing lung hypoplasia. from netterimages

hernias are located posterolaterally and known as Bochdalek hernias, while hernias occurring more anteriorly are known as Morgagni hernias.

Self-study

1. Which statement is true?
   (A) The embryologic origin of the musculature of the diaphragm is the septum transversum.
   (B) Congenital diaphragmatic hernias occur due to defective fusion of the pleuroperitoneal membrane with the septum transversum.
   (C) Spinal nerves from C1-C5 migrate caudally with myoblasts of the septum transversum leading to phrenic nerve innervation of the diaphragm.

(D) The right pericardioperitoneal canal is larger than the left contributing to a greater incidence of right sided congenital diaphragmatic hernias.

2. What vertebral level does the aortic hiatus originate?
   (A) T8
   (B) T10
   (C) T12
   (D) L1

Answers

1. Which statement is true?
   (A) The embryologic origin of the musculature of the diaphragm is the septum transversum.
   (B) Congenital diaphragmatic hernias occur due to defective fusion of the pleuroperitoneal membrane with the septum transversum—CORRECT. Congenital diaphragmatic hernias occur when the pleuroperitoneal membranes fail to properly fuse. If abdominal viscera herniate, lung hypoplasia can occur.
   (C) Spinal nerves from C1–C5 migrate caudally with myoblasts of the septum transversum leading to phrenic nerve innervation of the diaphragm.
   (D) The right pericardioperitoneal canal is larger than the left contributing to a greater incidence of right sided congenital diaphragmatic hernias.
2. What vertebral level does the aortic hiatus originate?
   (A) T8
   (B) T10
   (C) T12—CORRECT. The diaphragm has three major apertures, including the aortic hiatus at the level of T12. The IVC hiatus is at the level of T8 while the esophageal hiatus is at the level of T10.
   (D) L1.

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General Aspects in the Pathology of the Diaphragm

Ammar Asban and Benjamin Wei

Key Points

1. The diaphragm is the main muscle of respiration with a unique muscular and tendinous structure.
2. Diaphragmatic pathologies can be congenital such as eventration, Morgagni and Bochdalek hernias or acquired, such paralysis and hiatal hernia.
3. Patients with diaphragmatic disease can be asymptomatic or present with respiratory and gastrointestinal symptoms.
4. Chest X-ray, ultrasound, CT scan and MRI are most commonly used to diagnose diaphragm pathologies.
5. Treatment of diaphragm pathology depends on the underlying condition and ranges from observation to diaphragmatic resection.

Introduction

The diaphragm plays a vital physiological and anatomical rule in breathing and is considered the main respiratory muscle [1, 2]. It has a complex structure with muscular components and central tendinous components. Anatomically, the diaphragm originates from the inner surface of the lower six ribs laterally, sternum anteriorly, and costal cartilage anteromedially [3]. It serves as barrier between intrathoracic and intraabdominal compartments. It has three main orifices: caval, aortic and esophageal, which allow structures to pass to and from the abdominal cavity. The blood supply to the diaphragm comes mainly from phrenic and pericardiophrenic arteries. The phrenic nerve, which originates at C3, C4, and C5, with most of the motoneurons located at the C4 level, is the main nerve supply to the diaphragm [3].

This chapter covers the most common diaphragmatic pathologies and highlights the most recent updates in diagnosing and treating patients with diaphragmatic problems.

Diaphragm Paralysis

Diaphragm paralysis is defined as diaphragmatic dysfunction due to the interruption of nerve signals through the phrenic nerve to the diaphragm. The incidence of diaphragm paralysis is unknown. This condition is different from diaphragm eventration, in which the muscular portion of the diaphragm is replaced with fibroblastic tissue in the former and remains intact in the later. It can be unilateral or bilateral. The underlying cause, patients' presentation, clinical evaluation will be discussed in this chapter.

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Unilateral Diaphragm Paralysis

Unilateral diaphragm paralysis is more common than bilateral paralysis. This type of paralysis is often discovered incidentally on a chest radiograph. In normal breathing, during inspiration, the caudal movement of the diaphragm pushes the abdominal viscera downward and generate negative pleural pressure. Consequently, air enters into the lungs. Inspiration is also aided by other inspiratory muscles such as the sternocleidomastoid, serratus anterior and external intercostal muscles. The paralyzed hemidiaphragm, however, is redundant and floppy, and paradoxically moves up during inspiration. This is because the negative pleural pressure generated by the contralateral normal hemidiaphragm draws air from the other side of the chest, the paralyzed side. This respiratory impairment, however, tends to improve over time due the decrease in the compliance of the paralyzed hemidiaphragm. Unilateral diaphragm paralysis can be caused by phrenic nerve injury after heart surgery secondary to cooling and over stretching (mostly of the left phrenic nerve that runs within the posterior pericardium on the left pulmonary or other neoplasm or stretch injury due to hyperextension of the neck) [4, 5]. Additionally, unilateral diaphragm paralysis has been associated with viral infection such as Herpes zoster and poliomyelitis, neck trauma or surgery, scalene nerve blocks, compressive cervical tumor, cervical spondylosis, and pneumonia [6, 7]. Diaphragm paralysis may also be idiopathic, with no obvious antecedent cause (Ref scanned book). At rest, patients are usually asymptomatic. However, patients may experience dyspnea when they exercise or are in the supine position, or may experience difficulty sleeping or dyspnea when there is a concomitant underlying lung disease such as asthma exacerbation, COPD, or pneumonia [8–10]. Diagnosis of unilateral diaphragm paralysis is suspected in patients with an elevated hemidiaphragm in upright full-inspiration chest X-ray. However, this finding is not specific for paralysis; the differential diagnosis includes diaphragm eventration, subpulmonic effusion, and subphrenic abscess. Diaphragmatic fluoroscopy or ultrasound can be used to confirm unilateral diaphragm paralysis. Paradoxical movement of the paralyzed diaphragm is visualized while the patient is sniffing vigorously (hence its colloquial description as a "sniff test"). However, paradoxical movement is not found in all cases of diaphragm paralysis; the affected diaphragm may exhibit weak or no motion, but not paradoxical movement [11]. MRI and CT scan also can be used to exclude any underlying pulmonology pathology and/or tumor that could be impinging on or invading the phrenic nerve [12].

Although the findings of pulmonary function testing (PFTs) are nonspecific, PFTs can provide some objective evidence of the impact of diaphragmatic dysfunction in patients with dyspnea and a suspected paralyzed hemidiaphragm. These PFT findings are more consistent with a restrictive pattern and include reduction in the forced vital capacity (FVC) to 70–80 percent of predicted value that becomes more pronounced in the supine position. Additionally, a reduction of up to 60 percent of predicted value can be observed in the maximal inspiratory pressure (MIP) (normal values are more negative than -60 cm H_2O) with normal maximal expiratory pressure (MEP); the diagnosis can be confirmed by MEP/MIP of >2 [13]. Measurement of diaphragmatic thickness fraction using ultrasound can be used to diagnose diaphragm dysfunction in the pediatric population with suspected diaphragm dysfunction [14, 15]. To assess phrenic nerve integrity (complete or partial absence of signal), electromyography (EMG) can be conducted using either esophageal or surface electrodes [16, 17]. However, its routine use in unilateral paralysis is limited, as fluoroscopy is usually revealing of the diagnosis [18]. Measurement of transdiaphragmatic pressure will be discussed in further detail later in this chapter, under bilateral diaphragm paralysis. However, both, the maximal inspiratory force (Pdi-max) and the gastric (Pga) components of the Pdi will be decreased in unilateral diaphragm paralysis.

Asymptomatic diaphragmatic paralysis does not warrant intervention. Diaphragm plication may be required for symptomatic patients to improve dyspnea, orthopnea, and exercise tolerance. Before surgical intervention, an observation period of 6–24 months is recommended [18–20]. Spontaneous recovery may occur, although it is unlikely, especially after phrenic nerve injury during cardiac surgery [21]. During this time, however, exercise therapy may lead to improvement or resolution of symptoms and render surgery unnecessary [22]. Diaphragm plication can be done by either open or minimally invasive approaches, via the thorax or abdomen [23]. VATS diaphragm plication has been shown to be safe and effective with excellent outcomes compared to thoracotomy [19, 24]. If no obvious antecedent cause for phrenic nerve injury is determined, cross-sectional imaging to exclude any underlying neoplasm is required prior to diaphragmatic plication [19].

The decision about when to intervene and perform plication for diaphragm paralysis after cardiac surgery and phrenic nerve injury remains controversial. In a larger retrospective study, Floh et al. found an ultrasound-detected incidence of diaphragm paralysis of 2.5% (161 patients) among pediatric patients who have had cardiac surgery. Of those, 19% underwent plication. The author concludes that "early plication is associated with reduction in all intervals of care" [25]. In a review article of 13 studies that included 161 patients who underwent diaphragm plication for unilateral diaphragm paralysis, the author concluded that plication improves PFT, shortness of breath and functional status. Additionally, though a similar complication rate was found between the thoracotomy group and the VATS group, there was a higher mortality rate among those in the thoracotomy group (4% vs. 0%) [26]. Early and long term follow up after diaphragmatic plication demonstrates that the operation is associated with long term improvement in dyspnea, PFT and functional status as well as quality of life [18, 20, 27].

Bilateral Diaphragm Paralysis

The incidence of bilateral diaphragm paralysis is less common than the unilateral type. It most commonly caused by disease processes that involved the spinal cord or phrenic nerve at its origin such as a spinal cord tumor or transection, cervical osteoarthritis; peripheral nervous system disease processes such as post-viral neuropathy, diabetic neuropathy, Guillain-Barré syndrome; neuromuscular diseases such as myasthenia gravis [28, 29]. Eaton Lambert Syndrome; or muscular diseases such as polymyositis, dermatomyositis, and inclusion body myopathy.

Patients with bilateral paralysis are heavily dependent on their accessory respiratory muscles (scalenes, sternocleidomastoids). In contrast to unilateral diaphragm paralysis, patients with bilateral paralysis are usually symptomatic. However, the severity of symptoms depends on patients' age, function of accessory respiratory muscles and presence of any underlying pulmonary disease. Symptoms include exertional dyspnea, and orthopnea, and in advanced cases, respiratory failure, severe pulmonary hypertension and cor pulmonale may be observed. These findings may be mistaken for heart failure, but the work up for underlying heart disease is usually negative. Additionally, patients may experience morning headache, fatigue, hypersomnolence, and memory loss [30]. Symptoms are more severe in infants because they depend on their respiratory muscles to stabilize the compliant chest and because they typically are in a supine position [30] (Ref). Physical findings include tachypnea, paradoxical abdominal wall retraction, and hypoxemia as well as hypercapnia secondary to the atelectasis of the lung.

Similar to unilateral diaphragm paralysis, the diagnosis can be suspected in patients with dyspnea and elevated hemidiaphragms in the upright anteroposterior and lateral chest X-rays. However, it can be difficult to confirm the diagnosis since both hemidiaphragms are elevated. A sniff test will reveal a non-moving diaphragm or paradoxical movement during

respiration. This test can be confirmatory; however, a false-negative result can be observed in patients who recruit their expiratory muscles [31, 32]. A pulmonary function test shows restrictive patterns with reduction of the forced expiratory volume in 1 second (FEV1) and of the vital capacity to 45–50% of predicted values [33, 34]. These two values will decrease even more in the supine position due to the cephalad pressure applied by abdominal contents to the paralyzed diaphragm. Additionally, MIP can differentiate between patients with generalized muscle weakness and patients with diaphragmatic paralysis; the MIP will be lower than 60 cm H_2O in patients with bilateral paralysis, as opposed to greater than 60 cm H_2O in those with muscle weakness. Furthermore, screening for diaphragmatic dysfunction can be done by obtaining the ratio of MEP over MIP (MEP/MIP) [13]; this test has a sensitivity of up to 85% when a threshold ratio of 3 is used [3]. Ultrasound can identify the direction of diaphragm movement (no active movement during inspiration and paradoxical movement with sniff test) as well as reveal decreased amplitude [35, 36]. Furthermore, ultrasound can measure diaphragm muscle thickening during inspiration and it has been shown to be a useful tool in assessing potential recovery from diaphragm weakness [37]. Bilateral diaphragmatic paralysis can be confirmed by measuring transdiaphragmatic pressure (Pdi), which is considered the gold standard test [3, 38]. Two catheters are placed: one in the esophagus (measuring pleural pressure, Ppl) and the other in the stomach (measuring gastric pressure, Pga). The pressure differential between the two locations created by the diaphragm's activity can be measured at rest, at the end of inspiration or expiration, during deep breathing or sniffing, These values suffer from effort-dependent variation. Transcutaneous stimulation of the phrenic nerve yields a more consistent result, but can be uncomfortable. A Pdi of <15 cm H_2O with phrenic nerve stimulation generally indicates diaphragm dysfunction [38, 39]. Additionally, if the integrity of the phrenic nerve needs to be assessed for possible pacing, diaphragmatic EMG can be obtained. EMG may be able to reveal either a neuropathic or myopathic pattern of the paralysis [16, 17]. Due to its invasive nature and expertise needed to perform it, however, EMG is not routinely obtained for diaphragmatic paralysis evaluation. Blood gas can be obtained as well to evaluate the severity of ventilation-perfusion mismatch, which usually shows an increase in the partial pressure of carbon dioxide (PCO_2) and hypoxemia. Patients with diaphragm paralysis may have a coexisting sleeping disorder. Therefore, an overnight polysomnography may be recommended.

Treatment of bilateral diaphragmatic paralysis ranges from noninvasive conservative approaches to more invasive surgical intervention depending on etiology, disease severity and presence of underlying pulmonary disease. Noninvasive positive pressure ventilation (NPPV), with bilevel positive airway pressure (BPAP), can improve symptoms and quality of life even among patients with cor pulmonale, preventing respiratory failure [40]. It also can be used as a temporary measure while waiting for the diaphragm to recover after an iatrogenic or a traumatic injury to phrenic nerve [41–43]. Bilateral surgical plication has been described in literature with good short-term and long-term outcomes [44]. Versteegh et al. reported a 5-year follow up of 22 patients with unilateral (17 patients) and bilateral paralysis (5 patients) post plication with significant improvement of PFTs, quality of life, and dyspnea [45].

Diaphragm pacing has been described for patients with intact phrenic nerve function, but loss of central nervous input causing diaphragmatic paralysis. A higher success rate and better quality of life were achieved among those with complete spinal cord injury (above C3) when compared to those on mechanical ventilation [46]. Among carefully selected patients, diaphragm pacing has been shown to improve pulmonary function status and quality of life, weaning of ventilation, and resumption of some normal activities [47]. Patients with phrenic nerve lesions who are not candidates for diaphragm pacing can undergo surgical nerve transfer and autotransplantation simultaneously with

diaphragm pacing. Preliminary results have been shown that this can reduce the need and/or duration of ventilator support [48, 49]. Intermittent mechanical ventilation with cuirass respirators has demonstrated the improvement of respiratory status in some studies among patients with CO_2 retention and central hypoventilation [31]. In cases of life-threatening respiratory failure, endotracheal intubation or tracheostomy may be required.

Diaphragm Eventration

Eventration is a pathological condition in which the muscular potion of the diaphragm has failed to develop, leaving a thin layer of fibroblastic tissue that bulges into the chest. It can be congenital (failure of the diaphragm to properly develop due to abnormal myoblast migration to the septum transversum and the pleuroperitoneal membrane) or acquired, secondary to phrenic nerve injury [50–52]. The left side of the diaphragm is most commonly affected, particularly the anteromedial area. Eventration can be partial or complete. In partial eventration, only part of the diaphragm is affected (anterior, medial or posterolateral). On the other hand, the whole diaphragm is involved in complete eventration and this can be difficult to differentiate from diaphragm paralysis on chest radiograph. Diaphragm eventration has an incidence rate of 0.05%, with male predominance [53]. Infants usually present with respiratory distress, failure to thrive, and feeding difficulty. Adults are usually asymptomatic; however, symptoms such as dyspnea, chest pain, palpitations, dyspepsia, palpitation and recurrent pneumonia have, been reported [19]. Furthermore, hyperventilation and subsequent respiratory alkalosis secondary to ventilation/perfusion mismatch at the basal area of the lung may develop. Additionally, patients may complain of gastrointestinal symptoms such as epigastric pain or discomfort, as well as bloating. These symptoms may be aggravated by conditions that increase intra-abdominal pressure, such as strenuous exercise, obesity or pregnancy [54].

The majority of diaphragm eventrations are discovered incidentally on chest radiograph, which shows an elevated portion of the hemidiaphragm dome compared to the normal, opposite hemidiaphragm. When eventration is suspected, a CT scan or a fluoroscopy can confirm diagnosis with using a sniff test. In fluoroscopy, the diaphragm fails to descend either partially or completely. Additionally, paradoxical movement can be observed. A fluoroscopy sniff test can be used to distinguish between paralysis and eventration by demonstrating paradoxical movement of the paralyzed diaphragm which is absent in case of eventration [55]. However, some argue that the test has limited value due to the difficulty of interpretation, lack of specificity, and ultimately, the fact that both pathologies may respond to treatment with plication [55]. Ultrasound also can be used to assess diaphragm movement during respiration: inspiratory lag or small paradoxical movements can be observed [55, 56]. A CT scan can be used to distinguish eventration from other diaphragm pathologies such as tumor or subpulmonic pleural fluid. In the case of tumor, the contour of the diaphragm is more likely irregular at the dome, and the costophrenic angle is blunt in the case of subpulmonic pleural fluid. In diaphragm eventration, although there is a defect in the muscular portion of the diaphragm, the diaphragm maintains normal attachments to the sternum, ribs and spine [57]. In diaphragmatic paralysis, the muscular layer of the diaphragm exists, although atrophied; this layer is almost always absent in true eventration.

Treatment of diaphragm eventration is indicated only for symptomatic patients with the ultimate goals being relieving dyspnea and improving quality of life. This can be achieved by surgical repair with plication, which was first described in 1923 by Morrison [58]. Different approaches for diaphragm eventration repair include transthoracic, transabdominal, open, or minimally invasive, which have demonstrated comparable short-term results [55, 59, 60]. In one prospective study that including 12 patients with diaphragmatic eventration who were treated with video-assisted thoracic

surgery (VATS), VATS has been shown to be safe and effective as a treatment approach when compared to conventional methods. All patients experienced relief of their symptoms and good long-term results [19]. Several complications post diaphragm plication have been described in literature including pulmonary complication such as pneumonia, pleural effusion, and pulmonary emboli, as well as cardiac complications such as arrhythmia and myocardial infarction, in addition to abdominal compartment syndrome, abdominal visceral injury and gastrointestinal hemorrhage [55]. Furthermore, diaphragm plication in patients with morbid obesity and neuromuscular disorders is associated with technical challenges, higher complications and limited benefit [20, 55]. Therefore, it is recommended that these patients should be approached with extreme caution [55].

Diaphragm Hernias

Diaphragmatic hernia can be a congenital hernia through the foramen of Bochdalek or the foramen of Morgagni, or an acquired hiatal hernia. The general aspects of the underlying pathophysiology, clinical presentation, and diagnosis both diaphragmatic hernias will be discussed in this chapter. Treatment options and surgical approaches will be discussed in further detail in later chapters.

Congenital Diaphragm Hernias

Bochdalek Hernia

The Bochdalek hernia is a developmental abnormality of the posterolateral foramen of the diaphragm that was first described in 1848 by Bochdalek [61]. It is the most common of all congenital diaphragm hernias (95%), with a prevalence rate of 6% and an annual incidence of 1:2000–1:12,500 live births and only 0.17% incidence in adulthood [62–64]. A total of 368 cases were reported in a recently published review article of all published literature on Bochdalek hernias diagnosed in adulthood from 1955 to 2015 [64]. The mean age of these cases was 51 years and the majority of the subjects were male [57]. Bochdalek hernias can be discovered at any age, but are most commonly diagnosed in children. Adults may acquire these hernias by reopening of the pleuroperitoneal ducts due to precipitating factors, such as pregnancy, childbirth, persistent cough, chronic constipation, or vigorous physical activity [64]. Bochdalek hernias are most commonly located on the left side and contents can include colon (63%), stomach (40%), omentum (39%), and small bowel (28%) [64]. Less commonly, the pancreas, kidney, and spleen can be found as well [64]. Patients with right-sided hernias are usually asymptomatic because of the protective nature of the liver, while those with left-sided hernia are more likely tp present with abdominal pain, nausea, vomiting, or obstructive or pulmonary symptoms [65, 66]. Chest radiograph can be ordered first and may show air/air-fluid level above the diaphragm; however, a diagnosis of Bochdalek hernia cannot be excluded with a negative chest radiograph. CT scan remains the gold standard for the diagnosis of a Bochdalek hernia and three-dimensional CT has the advantage of visualizing the defect [66]. For upper gastrointestinal anatomy delineation and exclusion of any malrotation, upper gastrointestinal study can be obtained [62, 67]. Less commonly used to diagnose Bochdalek hernias are MRI and ultrasound. Given the likelihood of complications and wide range of presenting symptoms, most experts in the field recommend surgical repair for all Bochdalek hernias including asymptomatic patients as long as the patient is a good candidate to undergo surgical repair [62, 68, 69]. This can be done in a trans-abdominal or trans-thoracic fashion with open or minimally invasive approaches, with or without mesh.

Morgagni Hernia

The Morgagni hernia was first described by Morgagni in his book Seats and Causes of

Diseases, which was published in 1761 [70]. It is considered a rare entity with a reported prevalence rate of 3% among all diaphragm hernias [71]. It is more commonly diagnosed in adults than children. This congenital defect is y found in the anterior aspect of the diaphragm between the muscle fibers of the xiphisternum and the costal margin, and is most commonly reported on the right side (90%) [72, 73]. The hernia may contain omentum and or colon which is found in a peritoneal sac, and rarely other organs such as stomach, small bowel, and liver as well [74]. Most patients with Morgagni hernias are asymptomatic, while some present with pulmonary symptoms, gastrointestinal symptoms (dysphagia, bleeding, and GERD), or pressure and discomfort at the epigastrium and/or chest. The majority of patients are females, but men tend to present with symptoms earlier than women [74]. The disease is congenital, but predisposing factors such as obesity, pregnancy, and trauma play an important role in disease presentation and manifestation. Morgagni hernias are usually discovered incidentally on chest X-rays obtained for other reasons. Depending on the contents of the hernia, findings range from air-fluid contents or bowel gas patterns above the diaphragm in case of stomach or colon herniation, to homogenous opacity in the right cardiophrenic angle in case of omental herniation [75]. "Sign of the cane handle" is a radiologic finding accompanying Morgagni hernia so-called because of the resemblance to a profile of a cane handle on lateral chest X-ray. Diagnosis is confirmed with a CT scan, which will reveal air or contrast-containing viscous or mass density herniating through an anterior diaphragmatic defect. Complications such as obstruction and strangulation can result from incarceration of bowel contents of a Morgagni hernia. Surgery is considered to be the definitive treatment for Morgagni hernias for both symptomatic and asymptomatic patients. This can be achieved with open or minimally invasive approaches though the chest or abdomen.

Acquired Diaphragm Hernias

Hiatal Hernia

In general, a hiatal hernia is defined as a protrusion of any intra-abdominal viscera (but typically the stomach) into the chest through the esophageal hiatus, the weakest opening of the diaphragm [76]. The prevalence of hiatal hernia depends on age, however, an overall prevalence of 10–50% of the population has been reported [77, 78]. Sliding hernias (type I), represents the majority of these hernias (95%), followed by type III hernias, then type II hernias [79]. The underlying etiology of hiatal hernias is still unclear. However, congenital weakness of the esophageal hiatus, as well as genetic components, may play a role in the development of these hernias [5, 80]. Several risk factors for hiatal hernias have been described in literature, including old age, trauma, collagen or skeletal system disorders, history of esophageal or gastric surgery, increased intra-abdominal pressure by obesity, pregnancy, chronic constipation, and chronic obstructive pulmonary disease with chronic cough [5, 79, 81]. The current classification system of hiatal hernias divides this type if hernia into four sub-types [80]. Type I or sliding hernia (gastroesophageal junction (GEJ) migrates into the thorax), type II (herniation of the gastric fundus into the mediastinum and the GEJ remains in the normal anatomic position), type III or mixed (combination of types I and II), and type IV (includes other intra-abdominal viscera along with the stomach migrating into the chest). Clinical presentation usually depends on the type and size of hernia, the space the hernia occupies and the development of complications. Patients with small type I hernias are usually asymptomatic. However, GERD symptoms such as heartburn, dysphagia and regurgitation may affect patients with type I hernias due to the incompetence of the lower esophageal sphincter. Additionally, other nonspecific gastrointestinal symptoms such as nausea, vomiting, postprandial fullness and epigastric pain have

been reported. Furthermore, patients can present with GI bleeding secondary to gastric ulceration, gastritis, or erosions (Cameron lesions) [77]. Large hernias can eventually compress the lungs and result in upper and lower respiratory symptoms such as cough, asthma, shortness of breath, hoarseness, pharyngitis and laryngitis [80]. Presentation with complications may occur as well such as volvulus, incarceration and strangulation, which require immediate surgical intervention.

Hiatal hernias may be discovered incidentally on chest radiography, barium swallow or endoscopy. Other diagnostic tools used in evaluating hiatal hernias include high-resolution manometry (HRM) and CT scan (Table 1) [79]. Barium swallow is very sensitive for paraesophageal hernias and has the advantage of determining the size and location of the hernia, gastroesophageal (GE) junction position and stomach orientation. Upper endoscopy is an essential element in the diagnosis and preoperative work-up for hiatal hernias. A distance of at least 2-cm or more from the squamocolumnar junction and the diaphragmatic impression is diagnostic for sliding hiatal hernia at endoscopy. Furthermore, in paraesophageal hernias, a herniated stomach at the hiatus can be visualized by retroflexing the endoscope. Additionally, the consequences of long-standing GERD such as esophagitis, Barrett esophagus or neoplasm can be identified as well. High-resolution manometry offers the ability of real-time or dynamic evaluation of the EGJ and its components. Moreover, intermittent herniation not apparent by endoscopy or barium swallow can be identified with HRM. A recent study has shown a superior diagnostic sensitivity (94%) and specificity (91%) of HRM compared to upper endoscopy and barium study for detection of hiatal hernias when LES– crural diaphragm (CD) axial separation is greater than 1.2 cm [82]. The use of pH testing in hiatal hernia evaluation is not universal, however, preoperative evaluation of esophageal acid exposure with pH testing among patients with sliding hiatal hernias is recommended [83]. Additionally, CT scan is a great tool in identifying the hernia contents, direction and size which may affect preoperative planning.

Asymptomatic sliding hernias do not warrant surgical repair [83]. Those with reflux disease can managed medically, although the

Table 1 Diagnostic approaches for hiatal hernia

Diagnostic techniques	Preoperative evaluation	Advantages	Complications
Barium swallow radiography	Relevant for: esophageal contractions and stricture formation; adenocarcinoma; symptoms of GERD	Detects and assesses spontaneous and voluntary GERD	Hazards associated with radiation; unsuitable for barium or iodine hypersensitivity; inadvisable in pregnancy
CT scan	Mainly executed for visualizing gastric volvulus or size/contents of hernia; suitable for symptoms discrete from GERD	Visualizes alteration in gross structural features involved in GERD and fat deposition in the mediastinum	Not an ideal and precise technique for detecting esophageal hiatal hernia
Endoscopy	Symptoms specific for GERD; swallowing difficulty; hemorrhage	Appropriate for detecting sliding hiatal hernia and the stretching and enlargement of hiatus	Changes of inflammation; gas insufflation into the abdomen may increase the diameter of the hernia
High-resolution manometry	Recommended for evaluation of small/medium sized hiatal hernias; optional for large hiatal hernias	Evaluates quality of peristalsis, can affect decision for fundoplication	Uncomfortable for patient; can be difficult to pass probe in large hiatal hernias or extremely dilated esophagus

combination of GERD and sliding hernia may warrant surgical repair if better control of reflux is desired. See section "Hiatal Hernia".

Diaphragm Tumors

Diaphragmatic tumors are rare, with roughly 200 cases reported in the literature [84]. Females are slightly more affected than males, with a mean age of presentation of 40 years. Both sides of the diaphragm are equally affected. Patients most commonly present with symptoms such as cough, dyspnea, chest or abdominal pain/discomfort or hiccup. Incidental presentation has been observed in 15% of patients with benign tumors and 11% of patients with malignant tumors [85].

Primary and Secondary Benign Diaphragm Tumors

Primary benign tumors of the diaphragm may be cystic or solid. The most common benign cystic lesions of the diaphragm are mesothelial and bronchogenic cysts. Both type of cysts are congenital in origin and most commonly found in children. However, adult cases have been described. Very rarely, hydatid cyst secondary to Echinococcus granulosus can be found in the diaphragm as well [86]. Diagnosis of diaphragmatic cyst can be done by ultrasound, CT scan or MRI. See Table 2. With the exception of hydatid cysts, the consensus in the literature is to observe patients with diaphragmatic cysts who are asymptomatic; surgical resection should be preserved for symptomatic patients. Patient with diaphragm hydatid cyst should undergo complete surgical resection, followed by diaphragmatic repair. Patients should also receive albendazole afterward [87]. Many solid benign tumors of the diaphragm such as lipoma, neurofibroma angiofibroma, fibroma, hemangioma, schwannoma, chondroma, and hemangioendothelioma have been reported [88, 89]. Lipoma is the most common solid benign tumor of the diaphragm, and appears as a heterogeneous enhancing solid lesion with fat and septae of connective tissue on CT scan [85]. Although asymptomatic patients can be observed, some argue that due the possibility of transformation of into liposarcomas, complete resection should be pursued in these patients [90, 91].

Secondary benign diaphragmatic tumors are rare as well with endometriosis being the most common. This involves deposition of endometrial cells on the diaphragm, mostly on the right side. Patients can present with catamenial pneumothorax, hemothorax, or hemoptysis around the menstrual period [92, 93]. Surgical treatment by diaphragmatic excision and repair is recommended [94, 95].

Primary and Secondary Malignant Diaphragm Tumors

Diaphragmatic tumors are either primary, originating from the diaphragm, or secondary, due to invasion from adjacent structures or seeding in cases of metastases. Most common reported

Table 2 Imaging finding of each of the most common diaphragmatic cysts

Images	US	CT	MRI
Mesothelial cyst	thin-walled cystic structure	Homogeneous, nonenhancing, well-defined cysts of water density	Thin-walled cystic structure attached to the diaphragm
Bronchogenic cyst	Hypoechoic lesion	Linear and nodular calcifications along the cyst wall with soft tissue density within the lesion	Fluid-containing lesion
Hydatid cyst	Cyst with multiple vesicles	Mass lesion with solid and cystic components	Cystic structure with multiple vesicles inside

primary malignant tumors are rhabdomyosarcoma, leiomyosarcoma, malignant schwannoma, fibrosarcoma, neurofibrosarcoma, chondrosarcoma, and yolk sac tumor [84]. They are usually seen in chest images as smooth or lobulated soft tissue abutting the basal areas of the lung [5]. Both rhabdomyosarcoma and leiomyosarcomas are rare tumors of the diaphragm. They appear as heterogenous masses on CT scan. Rhabdomyosarcoma can be resected surgically followed by adjuvant chemotherapy, or treated with induction chemotherapy then resection in cases where the tumor is large or otherwise difficult/impossible to resect [85, 96, 97]. Surgical resection is the only treatment for leiomyosarcoma.

Secondary malignant tumors of the diaphragm can be a result of direct invasion from nearby organ such as lung (0.5% of lung cancer), pleura (mesothelioma), esophagus or intraabdominal organ, drop metastasis from mediastinal thymomas, or distant metastases such as ovarian cancer. Depend on the nature of the tumor and burden of the disease; diaphragmatic invasion can be treated with surgical resection with or without chemotherapy depending on the original site of the tumor and pattern/location of occurrence [84, 85].

Self-study

1. Which one the following hernias is the most common congenital diaphragmatic hernia:
   A. Bochdalek Hernia
   B. Morgagni Hernia
   C. Hiatal Hernia
   D. None of the above

   Correct answer is A. The Bochdalek hernia is a developmental abnormality of the posterolateral foramen of the diaphragm. It is the most common of all congenital diaphragm hernias (95%), with a prevalence rate of 6%.
2. Sniff test is described as a paradoxical movement of the paralyzed diaphragm that is visualized on fluoroscopy or ultrasound while the patient is sniffing vigorously?
   A. True
   B. False

   Correct answer is A: Sniff test can be used to assess diaphragm movement. However, paradoxical movement is not found in all cases of diaphragm paralysis; the affected diaphragm may exhibit weak or no motion, but not paradoxical movement
3. Which of the following statement about diaphragm eventration is CORRECT?
   A. A pathological condition in which the muscular potion of the diaphragm has failed to develop and replaced layer of fibroblastic tissue
   B. It is a congenital pathology only
   C. Incidence rate of 5%
   D. Treatment is indicated for all patients with diaphragmatic eventration, symptomatic or asymptomatic

   Correct answer is A: Eventration is a pathological condition in which the muscular potion of the diaphragm has failed to develop, leaving a thin layer of fibroblastic tissue that bulges into the chest. It can be congenital or acquired with incidence rate of 0.05% and treatment is indicated for symptomatic patients only.

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Diaphragmatic Hernias

C. Taylor Geraldson and Benjamin Wei

Introduction

Beyond serving as the major locomotive of respiration, pressure exerted by the diaphragm contributes to multiple physiologic tasks which utilize the Valsalva maneuver. As with any natural pressure barrier, contents on the side of higher pressure may find their way to the other side via the path of least resistance, whether that be a physiologic aperture (i.e. paraesophageal hernia), a congenital defect, or a traumatic opening. In any of these circumstances, surgical intervention is often warranted to restore the natural boundary of the diaphragm in order to optimize cardiorespiratory function, protect vascular integrity of the herniated organ, and preserve luminal patency of any tubular structures.

Pathologies of the diaphragm include eventration, hernias, and porous syndromes. Surgery on the diaphragm may be conducted for those reasons, and also occasionally for traumatic and oncologic purposes. Surgical approaches from the chest, the abdomen, or both via thoracoabdominophrenotomy are variously employed depending on the specific clinical circumstances and thus the thoracic surgeon must be well versed in the relevant surgical anatomy to maintain a full clinical arsenal. These approaches are traditionally performed via open techniques, however laparoscopic, thoracoscopic, and now robotic techniques have more recently been employed based on the same principles. With any approach, core and neighboring structures must be considered and respected to gain optimal outcomes and prevent inadvertent injury.

Surgical Anatomy

Structure

Domed in shape, the diaphragm consists of a central tendinous portion which is noncontractile and circumferentially serves as the insertion of the ringed, outer muscular portion. Origins of the muscular portion of the diaphragm are drawn from the lumbar spine posteriorly, the lower sternum and xiphoid process anteriorly, and the bilateral lower ribs. The natural gaps between these muscle origins, named Morgagni anteriorly and Bochdalek posteriorly, contribute to diaphragmatic hernias described later in this text.

Arterial and Venous Anatomy

Above the diaphragm, the arterial supply of the diaphragm comes from paired superior phrenic arteries which arise from the inferior

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thoracic aorta, crossing over each respective crus as they emanate from the posterior diaphragm. Below the diaphragm, paired inferior phrenic arteries cross below each respective crus in much the same way. The origin of the inferior phrenic arteries is subject to more variation and may arise alone or together from the supra celiac aorta, the celiac trunk, each alone from the renal arteries, or some combination of these [1]. Moving dorsal to ventral, the phrenic arteries will anastomose with small diaphragmatic branches from the internal mammary and intercostal arteries. The diaphragmatic venous system largely mirrors the artery anatomy, primarily draining to the azygos and hemiazygos above the diaphragm and the inferior vena cava below. The clinical significance of this rich and redundant blood supply is that, away from the major branch origins, the diaphragm may be incised and sutured without concern for ischemic injury.

Innervation

Paired diaphragmatic nerves arise from the roots of the cervical plexus at the C3-5 levels and traverse down the neck, crossing the anterior scalene muscle in a lateral to medial fashion and are situated medial to the subclavian artery on entering the thoracic cavity. The positional course of the phrenic nerve relative to the internal mammary arteries is subject to variability, running medial to the internal mammary artery slightly more than half of the time on the left and slightly less than half the time on the right [2]. In either case, the phrenic nerve course must be considered due to the risk of injury during internal mammary harvest for coronary revascularization. As it courses inferiorly, the left phrenic nerve runs lateral to the aortic arch and along the lateral aspect of the pericardium before branching over the left hemidiaphragm. Similarly, the right phrenic nerve runs along the lateral aspect of the innominate vein, SVC, pericardium, and cranial IVC before branching over the right hemidiaphragm. The intradiaphragmatic course of the phrenic nerves and their branches are within the muscle and for that reason not easily observed intraoperatively. The sentinel, and often referenced, paper by Merendino and colleagues from 1956 lays out the intradiaphragmatic course [3]. In short, each phrenic nerve divides into an anterior and posterior trunk. The anterior trunks subdivide into sternal and anterolateral branches, while the posterior trunks similarly divide into crural and posterolateral branches. The anterolateral and posterolateral branches run peripherally along the central tendon near the fibromuscular insertion and take the shape of handcuffs/manacles which is pertinent when planning phrenotomy [4].

Pathologies

Diaphragmatic Elevation

Abnormal elevation of the diaphragm, called eventration, may be due to a congenital malformation or an acquired phrenic nerve palsy. Congenital eventration is caused by abnormal colonization of diaphragmatic myoblasts which result in a grossly thin, translucent membrane which, on microscopic analysis is composed of two serous layers [5]. Acquired eventration secondary to phrenic nerve paralysis may occur at any stage of life for virtually any reason.

Whether congenital or acquired, diaphragmatic eventration results in the same physiologic consequences of reduced lung volume and suboptimal respiratory mechanics. The clinical presentation of diaphragmatic eventration runs the gamut from respiratory failure requiring mechanical ventilation within hours of birth to asymptomatic incidental diagnosis in adulthood.

Categorization of Diaphragmatic Hernias

Diaphragmatic hernia defects may be generally separated into categories of congenital, acquired, and post-traumatic/post-surgical. Acquired diaphragmatic defects, are the result of

chronic enlarging of physiologic apertures (i.e. hiatal and paraesophageal hernias). Acquired diaphragmatic hernias will be covered in another section of this text.

Development of Congenital Diaphragmatic Hernias

The formation of the diaphragm begins during the 3rd week of gestation through the joining of the septum transversum anteriorly, the paired dorsolateral pleuroperitoneal folds, and the dorsal mesentery. While the final diaphragmatic structures do not all 100% correlate to single, discrete embryologic origins, the central tendon is formed from the septum transversum and the dorsal mesentery contributes the diaphragmatic crura. Ultimately, these embryologic structures are joined by the 7th week of gestation. However, the pleural and peritoneal cavities remain in communication via right and left pleuroperitoneal ducts until the pleuroperitoneal membranes are closed by gestational week 8. While, cervical myotomes 3–5 contribute the innervated muscular portion of the diaphragm, the joining of the developing diaphragm to the body wall occurs during gestational weeks 9–12, forming the diaphragmatic recesses and explaining why the peripheral diaphragm does receive some innervation from the lower intercostal nerve bundles.

Around gestational week 8, the intestines migrate from the yolk sac to the abdomen. Alterations to the normal timetable of this migration and diaphragmatic development result in congenital diaphragmatic hernias.

Failed closure of the pleuroperitoneal ducts on either side results in a Bochdalek defect. Failed fusion of the septum transversum to the sternum results in the Morgagni defect.

Porous Diaphragm Syndrome

Porous diaphragm syndrome is a unifying concept advocated by Dr. Kirschner to relate physiologically differing pathologic processes whereby there is passage of fluid across the diaphragm [6]. Dr. Cerfolio suggests a clinical diagnosis of exclusion for the syndrome as the presence of a large pleural effusion (>500 mL) in a patient with no cardiopulmonary disease or any other causal pathology [7]. A pleural effusion is certainly not required for diagnosis, as the syndrome is also frequently related to catamenial pneumothorax, pneumothorax secondary to laparoscopic insufflation, and other entities. The right sided predominance for diseases related to porous diaphragm syndrome is suggested by Dr. Kirschner to be due to a piston-like action of the liver on the right hemidiaphragm [8].

Phrenotomy

While physiologically unique, for the purpose of phrenotomy the diaphragm may be treated as any other muscle, and incisions may be carried out with any combination of sharp dissection and electrocautery so long as the operator accounts for the possibility of thermal injury near important structures. As with any three dimensional curvilinear surface, marking the natural alignment prior to incising will facilitate reapproximation. Traditionally this is performed with marking sutures or clips. For linear incisions, the use of linear cutting stapler can be used to simultaneously facilitate hemostatic division and marking for reapproximation. Additionally, staple line material may serve to buttress the reapproximation sutures.

Phrenotomy incisions fall into three groups: circumferential, radial, and along the central tendon.

Circumferential incisions, if appropriately peripheral, are advantageous in avoiding any major nerve branches. These incisions should be at least 5 cm away from the edge of the central tendon to comfortably avoid the anterolateral and posterolateral nerve branches. More peripheral circumferential incisions may be disadvantaged by length of incision and difficulty of closure.

Radial incisions of a diaphragm are useful not only for thoracoabdominal operations, but

also aide in retroperitoneal exposures, and are especially useful in gaining supraceliac control of aortic aneurysms. When undertaking a radial incision, care must be taken to direct the incision between the anterolateral and posterolateral nerve branches. This is best accomplished by taking a path from the midaxillary line toward the central aspect of the diaphragm. Deviation from such a line risks segmental diaphragm paralysis.

The central tendon incision is advantageous in that the risk of nerve injury is minimized. This incision may be undertaken from a thoracic or abdominal approach, but it is limited in utility as it provides only minimal exposure to the other side of the diaphragm.

Plication

Regardless of etiology, eventration may exert negative effects on pulmonary, cardiac, and digestive physiology. From a pulmonary standpoint, eventration decreases lung volume and worsens ventilation/perfusion matching. Cardiac function may be affected in cases of severe left sided eventration which causes downstream dextrocardia and arrhythmias. Digestive effects of eventration include a weakened lower esophageal sphincter promoting GERD and Chilaiditi syndrome.

From the latin, *plicare*, meaning "to fold", diaphragmatic plication was among the first successful interventions on the diaphragm.

Principles of Repair

The goal of plication is to restore normal intrathoracic volume to the affected side, which in turn allows for improved respiratory mechanics and ventilation perfusion matching while minimizing effects of mediastinal and abdominal organ shifting. In circumstances of eventration secondary to phrenic nerve palsy, flattening the diaphragm via plication theoretically will provide improved respiratory mechanics via the preserved peripheral diaphragmatic innervation from intercostal sources.

Plication Techniques

Plication techniques are focused on the central aspects of the diaphragm. While a peripheral plication (such as a radial phrenotomy with overlapping reapproximation) would serve to flatten the diaphragm, it would potentially compromise intercostal/accessory innervation, which is especially important in cases of eventration secondary to phrenic nerve palsy.

The two most commonly advocated techniques are termed single pleat and multi pleat. Whichever technique is employed, the operator should begin by grasping the diaphragm with babcock clamps to assess diaphragmatic redundancy and visualize the optimal axis of plication and tension required based on individual patient anatomy.

The single pleat technique aims to bring a single fold of diaphragm back onto itself, resulting in a three layers of diaphragm in the area of greatest redundancy. Once axis and tension is determined, a line of simple horizontal mattress sutures are tied in place using permanent suture. Then, any remaining redundant diaphragm is plicated into another simple horizontal mattress row. This tacking layer should preferentially directed toward any thinned or weakened area of diaphragm to buttress it.

The multi pleat technique is sometimes referred to as the accordion plication, an apt descriptor for the appearance of the diaphragmatic tissue within the plication when tightened. In this technique, pledgeted horizontal mattress suture rows are placed along the axis of plication using double needle nonabsorbable suture. Beginning on the far side of the operative field and working back toward oneself, the operator may periodically draw slack out of the suture rows to determine the appropriate length of plication, at which point another pledget may be placed and the free ends knotted to give the desired degree of tautness.

Positioning and Approaches

Diaphragmatic plication is traditionally performed in open fashion via posterolateral thoracotomy, which permits optimal exposure to the middle and anterior diaphragm; however minimally invasive thoracoscopic approaches employ the same plication techniques and are preferred by many surgeons. The patient should be placed in lateral decubitus position. Placement of a double lumen endotracheal tube will facilitate exposure in open approach and is essential for thoracoscopic approach.

A variety of thoracoscopic approaches are employed at various institutions. Our preferred minimally invasive approach uses a camera port in the 8th intercostal space with a single larger working incision in the 5th intercostal space aided by an Alexis wound retractor (Applied Medical; Rancho Santa Margarita, CA). Optimal placement of the working incision is critical and is typically located in the 7th or 8th intercostal space anteriorly. The start of the horizontal mattress suture is placed in a posterolateral location and the knot may be tied by hand, or with the assistance of a thoracoscopic knot tyer. The suture is then run towards the incision, plicating the diaphragm so that it is taut. An additional row of plication can be performed as needed. Robotic diaphragmatic plication can be performed as well. Diaphragmatic plication can be performed via a transabdominal route as well, which may be an advantage if the chest is hostile; this may be done laparoscopically or robotically.

Congenital Hernia Repairs

As described in greater detail above, congenital diaphragmatic hernias occur secondary to failed fusion of the embryologic origin structures. The Bochdalek defect presents in approximately 1/2500–1/4000 live births, with an 85% left sided predominance [9]. Left sided predominance in clinical presentation is traditionally attributed to the embryologic diaphragm first fusing on the right. Neonatal presentation usually manifests itself with respiratory insufficiency and is associated with a high mortality.

Compared to neonates, clinical presentation of the Bochdalek hernia in adults is rare and symptoms may be either related to size and mass effect of hernia contents (i.e. respiratory, cardiac) or related to incarceration/strangulation of the hernia contents (i.e. gastric outlet obstruction, intestinal ischemia, hydronephrosis). Mullins et al. report a radiographic incidence of 0.17% after review of all abdominal computed tomography scans at a single institution over a one year period [10]. However, the majority of the hernias identified in that review contained only fat, with only 0.05% of patients with hernias containing enteral contents or solid organs. Interestingly, there was a right sided predominance of Bochdalek hernias in this study population, which confers a protective aspect to the liver in limiting progression of symptomatic or clinically significant right sided Bochdalek hernias.

Morgagni hernias more commonly present in adulthood, and with a right sided predominance secondary to protective benefit of the pericardium on the left [11].

Completely asymptomatic hernias containing only retroperitoneal fat or omentum may be observed, although serial imaging is recommended to determine if the hernia is enlarging over time. Congenital diaphragmatic hernias in the adult that containing abdominal viscera should be repaired on an elective basis to prevent risk of progression to obstruction and strangulation.

Considerations of Repair

Beyond the obvious principles of reduction and closure, there are many considerations when approaching repair of congenital diaphragmatic hernia for which there is no consensus and/or patient specific factors must be weighed. What is the optimal patient positioning? Will a double lumen endotracheal tube be required? Should the hernia be approached from the chest or the abdomen or combined? Should it be performed

open or is it amenable to laparoscopic/thoracoscopic repair? Should the sac, if present, be excised? Should mesh be used? These decisions often depend on individual patient anatomy and the experience of the surgeon.

Positioning and Airway

Whenever possible, positioning should facilitate exposure and reduction of an operation by gravity assistance. Thus, at least some degree of lateral decubitus positioning should be employed when preparing to repair the posterolateral Bochdalek defect. Some surgeons report using a 30 degree bump in the split leg position for laparoscopically approached Bochdalek repairs [12]. Use of steep reverse Trendelenburg position is also helpful during dissection and reduction in a laparoscopic approach. Consideration of possible conversion to open laparotomy or thoracotomy should be taken prior to draping on minimally invasive approaches. In thoracoscopic and open thoracotomy approaches, double lumen endotracheal tube placement should be attempted to facilitate visualization and exposure.

Approach

Abdominal approaches are favored in the emergent setting for because they allow for post-reduction inspection of the hernia contents and intervention for any nonviable strangulated components. A thoracic approach is superior in the setting of a small hernia defect, through which dissection and reduction via a transabdominal approach may be difficult due to visualization. If planning for a transabdominal approach, the surgeon should be prepared for thoracoscopy or thoracotomy to deal with intrathoracic adhesions.

Minimally Invasive Repairs

While generally avoided in the setting of strangulation, minimally invasive techniques for adult congenital diaphragmatic hernia repair are widely reported for elective repairs. Laparoscopic repair of adult congenital diaphragmatic hernia can be performed with a low morbidity rate and reduced hospital length of stay [13]. While most literature for minimally invasive repair focused on laparoscopy, some advocate a thoracoscopic approach, especially in the setting of a right sided hernia where the liver would interfere with a laparoscopic approach.

For the Morgagni hernia, we have had success in robot assisted repair using the da Vinci Si System (Intuitive Surgical; Sunnyvale, CA). We begin with the patient in the supine position. After obtaining insufflation via periumbilical laparoscopic entry, we place two additional working ports. Secondary to the lack of haptic feedback on current robotic systems, we favor a traditional laparoscopic reduction of hernia contents to better detect resistance and allow for safer tissue handling. After reduction of visceral contents and docking the robot, we proceed in primary closure of the Morgagni defect with pledgeted nonabsorbable sutures. In coordination with a bedside assistant armed with a Carter- Thomason Suture Passer (Cooper Surgical; Trumbull, CT), we place Teflon-pledgeted non-absorbable sutures in a horizontal mattress fashion. By exteriorizing the suture ends and tying them in extracorporeal fashion, we are able to ensure transfascial suture anchoring of the diaphragm. We then place a mesh underlay to reinforce the repair, and suture the bottom edge of the mesh to the abdominal wall with a continuous V-loc suture (Medtronic; Minneapolis, MN) [14].

Hernia Sac Excision

At times, diaphragmatic hernias will not possess a hernia sac, likely due to embryologic return of intestinal contents from the yolk sac prior to the closure of the pleuroperitoneal membrane. Some propose that rupture of the hernia sac is the sentinel event which progresses an asymptomatic hernia into a symptomatic hernia [15]. Morgagni hernias are more likely to have a hernia sac than

Bochdalek hernias [16]. While some authors advocate hernia sac excision prior to repair, other suggest it is unnecessary for adequate repair and only increases risk of pleural injury [17]. It is our own experience that the hernia sac, when present, is usually so insubstantial that any efforts beyond what is necessary to untether and reduce the vital contents of the hernia are impractical.

Mesh

Primary closure may not be possible due to the size of the defect, necessitating use of mesh incorporation. Additionally, mesh may used to reinforce a primary repair. A variety of mesh materials are available and have been employed. Some authors discourage use of polypropylene mesh secondary to pro-adhesion properties, and instead advocate the use of dual or biologic meshes around areas of sliding contact to prevent erosion into gastrointestinal structures. Mesh overlap and fixation techniques are widely varied with no high level evidence for use in diaphragmatic hernia repairs. Drawing from laparoscopic evidenced guidelines, mesh repairs should have 3–5 cm overlap [18]. Mesh may be fixed with sutures or stapling devices, however laparoscopic tacking devices should be avoided due to high number of complications reported in literature [19]. In most instances, we favor a primary repair with mesh underlay, secured with interrupted sutures superiorly and by a running suture at the inferior borders. In cases where the hernia defect abuts the chest wall, anchoring sutures should be placed around the appropriate rib.

Conclusion

Congenital diaphragmatic hernias in the adult represent a distinct surgical challenge. The variability of hernia size, contents, and other patient specific factors render each repair unique and dictate a thoughtful approach. Evolving technology in minimally invasive surgical modalities has benefitted the modern thoracic surgeon with a multitude of approach options. Regardless of approach and technology utilized, reliance on traditional surgical principles and core anatomy are key to a successful outcome.

Self-study

1. Which statement is true?
   (A) The embryologic origin of the musculature of the diaphragm is the septum transversum.
   (B) Congenital diaphragmatic hernias occur due to defective fusion of the pleuroperitoneal membrane with the septum transversum.
   (C) Spinal nerves from C1–C5 migrate caudally with myoblasts of the septum transversum leading to phrenic nerve innervation of the diaphragm.
   (D) The right pericardioperitoneal canal is larger than the left contributing to a greater incidence of right sided congenital diaphragmatic hernias.
2. What vertebral level does the aortic hiatus originate?
   (A) T8
   (B) T10
   (C) T12
   (D) L1.

Answers

1. Which statement is true?
   (A) The embryologic origin of the musculature of the diaphragm is the septum transversum.
   (B) Congenital diaphragmatic hernias occur due to defective fusion of the pleuroperitoneal membrane with the septum transversum—CORRECT. Congenital diaphragmatic hernias occur when the pleuroperitoneal membranes fail to properly fuse. If abdominal viscera herniate, lung hypoplasia can occur.
   (C) Spinal nerves from C1–C5 migrate caudally with myoblasts of the septum transversum leading to phrenic nerve innervation of the diaphragm.

(D) The right pericardioperitoneal canal is larger than the left contributing to a greater incidence of right sided congenital diaphragmatic hernias.

2. What vertebral level does the aortic hiatus originate?
   (A) T8
   (B) T10
   (C) T12—CORRECT. The diaphragm has three major apertures, including the aortic hiatus at the level of T12. The IVC hiatus is at the level of T8 while the esophageal hiatus is at the level of T10.
   (D) L1.

Self-study Questions

Phrenotomy incisions fall into which three groups?
   (A) median, medial, circumferential
   (B) central tendon, radial, circumferential
   (C) anterior, central tendon, posterior
   (D) anterior, circumferential, lateral
   (E) anterior, circumferential, oblique.

Correct answer is B: Phrenotomy incisions fall into three groups: circumferential, radial, and along the central tendon. Circumferential incisions, if appropriately peripheral, are advantageous in avoiding any major nerve branches. Radial incisions of a diaphragm are useful not only for thoracoabdominal operations, but also aide in retroperitoneal exposures, and are especially useful in gaining supraceliac control of aortic aneurysms. The central tendon incision is advantageous in that the risk of nerve injury is minimized, but it is limited in utility as it provides only minimal exposure to the other side of the diaphragm.

Diaphragmatic plication for left sided eventration is most safely focused on what anatomic area?
   (A) muscle lying medial to left-sided central tendon leaflet
   (B) muscle lying posterolateral to left sided central tendon leaflet
   (C) muscle lying anterolateral to left sided central tendon leaflet
   (D) left-sided central tendon leaflet
   (E) right-sided central tendon leaflet

Correct answer is D: Plication techniques are focused on the central aspects of the diaphragm. While a peripheral plication (such as a radial phrenotomy with overlapping reapproximation) would serve to flatten the diaphragm, it would potentially compromise intercostal/accessory innervation, which is especially important in cases of eventration secondary to phrenic nerve palsy.

Self-study Pathology Diaphragm

1. Which one the following hernias is the most common congenital diaphragmatic hernia:
   A. Bochdalek Hernia
   B. Morgagni Hernia
   C. Hiatal Hernia
   D. None of the above.

   Correct answer is A. The Bochdalek hernia is a developmental abnormality of the posterolateral foramen of the diaphragm. It is the most common of all congenital diaphragm hernias (95%), with a prevalence rate of 6%.
2. Sniff test is described as a paradoxical movement of the paralyzed diaphragm that is visualized on fluoroscopy or ultrasound while the patient is sniffing vigorously?
   A. True
   B. False.

   Correct answer is A: Sniff test can be used to assess diaphragm movement. However, paradoxical movement is not found in all cases of diaphragm paralysis; the affected diaphragm may exhibit weak or no motion, but not paradoxical movement
3. Which of the following statement about diaphragm eventration is CORRECT?
   A. A pathological condition in which the muscular potion of the diaphragm has failed to develop and replaced layer of fibroblastic tissue
   B. It is a congenital pathology only
   C. Incidence rate of 5%
   D. Treatment is indicated for all patients with diaphragmatic eventration, symptomatic or asymptomatic.

Correct answer is A: Eventration is a pathological condition in which the muscular potion of the diaphragm has failed to develop, leaving a thin layer of fibroblastic tissue that bulges into the chest. It can be congenital or acquired with incidence rate of 0.05% and treatment is indicated for symptomatic patients only.

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Approaches and Surgical Techniques in the Acquired Pathology of the Diaphragm

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Key Points

- Symptomatic diaphragmatic relaxation in adults as well as congenital phrenic nerve palsies resulting in respiratory distress can be surgically managed with a plication procedure completed via either a transthoracic or transabdominal approach. Minimally invasive techniques are preferred from a postoperative pain and recovery standpoint.
- Diaphragmatic tumors are rare and should be resected en bloc when technically feasible.
- Type I hiatal hernias should be managed based solely on associated symptoms, and surgical management only pursued if maximum medical therapy is unsuccessful.
- Although the majority of surgical management of symptomatic hiatal hernia is completed with the minimally invasive laparoscopic or robotic approach, the Collis-Belsey transthoracic approach remains an important consideration in patients who require reoperation, are known to have a esophageal shortening, or are requiring a simultaneous thoracic operation.

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Introduction

Aside from congenital issues, the diaphragm can be affected by acquired pathology. These issues include diaphragmatic relaxation or eventration of a weakened or paralyzed hemidiaphragm, tumors of the diaphragm, and esophageal hiatal hernia. The pathology and transthoracic surgical management of symptomatic individuals affected by these issues are described in this chapter.

Diaphragmatic Relaxation

In its most clinically significant presentation, diaphragmatic relaxation from phrenic paralysis or eventration due to congenital or age-related lack of muscle mass can cause respiratory compromise. Symptomatology for this inability to properly create negative pressure in the pleural cavity varies, ranging from mild increased work of breathing during activity to total respiratory compromise in children and infants. In adults, the most common cause of this relaxation is iatrogenic phrenic injury, but it can also be caused by trauma, tumor, and infection. Surgical management in appropriate candidates was first successfully accomplished in 1923 by Morrison [1]. The goal of the operation is diaphragmatic stabilization by surgical plication, which displaces the diaphragm inferiorly, permitting more room

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for lung expansion and mitigating paradoxical movement of the diaphragm from further compressing the lung.

Candidates for Surgery

When congenital eventration is diagnosed, care should be taken to assess the patient for other congenital anomalies. Smith et al. identified associated congenital abnormalities in seventy percent of affected individuals including heterotaxy with visceral transposition, cleft lip and/or palate, Werdnig Hoffmann disease, horseshoe kidney, or anomalies associated with Trisomy 18 [2]. This is especially important in young patients as lung hypoplasia can accompany diaphragmatic eventration. Surgical management should only be considered after more conservative approaches have been exhausted. In infants with eventration, this involves supplemental oxygen, elevation of the head of the bed, and nasogastric or post-pyloric feeding until the ribs and diaphragm musculature mature [3, 4]. Adults presenting with diaphragmatic relaxation often do not have any notable symptoms and the pathology is identified incidentally. In significantly symptomatic patients with dyspnea and poor oxygenation, especially those who have phrenic nerve compromise due to prior congenital heart defect repair, surgical repair can result in sustainable improvement in symptoms [5]. A chest CT is prudent as a part of the presurgical workup in patients without obvious antecedent event resulting in phrenic nerve injury, to rule out a potential mass or neoplasm along the course of the nerve.

Surgical Management

There are multiple plication techniques that can be applied to the surgical management of diaphragmatic relaxation, and they can be employed with open, thoracoscopic, or robotic techniques. Imbricating nonabsorbable stitches can be placed across the central tendon of the diaphragm, and when cinched down, fold the central tendon upon itself. This caudally displaces the dome of the diaphragm [5, 6]. Pledgets can used to decrease the risk of tearing through the muscle or central tendon, but are not necessary in all cases. A single-pleat technique can be more easily completed thoracoscopically, where a tool is used to depress the diaphragm inferiorly as two columns of continuous nonabsorbable suture are placed lateral to medially, and then cinched and tied. The diaphragm should be taut, but not overly so, at the end of the operation. Additional rows of plication sutures can be placed as needed to achieve this result. If visualization permits, a radial pattern of imbricating horizontal mattress sutures can be placed along the outer ring of the diaphragm to the muscular thoracic wall. This radial technique is often technically difficult or unfeasible due to how deep the thoracic space descends at its lateral edges. A single chest tube is generally all that is necessary at the end of the procedure, and an intercostal nerve block can be performed as an adjunct for postoperative pain control.

Postoperative Management

The patient should be weaned to extubation in the operating room, with an emphasis on avoiding significant "bucking" resulting in increased intraabdominal pressure that could stress the repair. The chest tube can be removed when there is no evidence of leak and output is demonstrated not to be overly bloody. We favor early removal of the chest tube, as soon as the afternoon of surgery, if possible. Postoperative chest radiograph should demonstrate improvement in diaphragmatic elevation on the side of the plication. This improvement is often most dramatic on the first postoperative film, even achieving a "lower than physiologic" result; this finding tends to even out and become more symmetric over time. Patients often notice a fairly immediate improvement in their dyspnea, although in many the benefits are not noted until later in the recovery process. At times, this benefit can even take 3–6 months to become apparent. Pulmonary function testing postoperatively does not need to be routinely performed, but if done, often demonstrates improvement in all measured

values. Versteegh et al. demonstrated significant improvement in vital capacity and forced expiratory volume in one second, as well as improvement of dyspnea [7]. Inadequate plication will result in no improvement in symptoms, while too much plication will result in excess suture line tension and repair failure [8]. In children, plication does not interfere with diaphragm development. In adults, patients undergoing plication for phrenic nerve dysfunction have lasting benefits from the procedure [9, 10].

Diaphragmatic Tumors

Primary diaphragmatic tumors are rare. Malignant primary tumors of the diaphragm are less common than benign lesions [11]. The most common malignant primary tumors of the diaphragm are rhabdomyosarcoma and fibromyosarcoma while the most common benign lesions are lipomas and cysts [12, 13]. Most diaphragm tumors are found in the fifth to seventh decades of life and they are generally asymptomatic. They are usually found incidentally either at the time of surgery or on routine imaging [14]. When symptoms do occur they usually include chest pain, dyspnea and cough [11].

Secondary tumors of the diaphragm are more common than primary diaphragm tumors. These occur when the diaphragm is invaded by malignant tumors that originated in surrounding structures. Secondary tumors of the diaphragm include lung cancer, malignant thymoma, and hepatic metastasis [15]. Additionally, the diaphragm can be a site of distant metastasis.

When technically feasible, all tumors of the diaphragm should be resected with reconstruction of the diaphragm. Computed axial tomography and magnetic resonance imaging are both adequate options for pre-operative visualization of diaphragmatic tumors [14]. Potential involvement of surrounding structures adjacent to the diaphragm should be considered during surgical planning. The tumor should be removed en bloc with the diaphragm and the diaphragmatic defect may be closed either primarily or more commonly, with mesh reconstruction [11].

Hiatal Hernia

Hiatal hernia describes herniation of abdominal cavity contents above the diaphragm into the mediastinum through the esophageal hiatal orifice. The most common symptom of this breach of anatomic boundaries is gastroesophageal reflux, although significant herniation can cause dysphagia, epigastric and chest pain, dyspnea, which can sometimes be postprandial in nature, or iron deficiency anemia if Cameron lesions develop.

Esophageal Hiatal Orifice Anatomy

The esophageal hiatal orifice is an elliptical opening in the diaphragm located approximately at the level of the T10 vertebra. Although it is a common misnomer to refer to the right and left sides of the hiatus as the right and the left crus, respectively, technically the hiatus is formed by only the right diaphragmatic crus, which originates from the anterior longitudinal ligament of L1–L3 vertebrae and splits around the esophagus to form the hiatus. The orifice is angled superiorly and anteriorly. Each hiatal muscular bundle has lateral fibers inserting at the central tendon of the diaphragm, and medial fibers, which form the hiatal margins and intercross anteriorly to the esophagus. The anterior and posterior vagal trunks travel with the alimentary tract through the hiatal orifice at this level. In normal anatomic configuration, the esophagus is anchored circumferentially to the diaphragm by the phrenoesophageal membrane. This membrane is formed by the fascia transversalis located on the underside of the diaphragm [16, 17].

Risk Factors

In a 2011 meta-analysis, Menon et al. found that age above 50 years is associated with hiatal hernia with an odds ratio of 2.17 with a 95% confidence interval 1.35–3.51 [18]. The phrenoesophageal membrane increases in laxity with age as the amount of elastic tissue declines and it is

exposed to more cumulative mechanical force; this makes older individuals more prone to herniation [17, 19]. Hiatal hernia is also associated with increased BMI; for individuals with BMI greater than 25 kg/m^2, the odds ratio of having a hiatal hernia was 1.93 with 95% confidence interval—CI—1.10–3.39 [18]. A recent case-control study of patients who underwent upper gastrointestinal endoscopy, when compared to controls with BMI less than 20, the relative risk of hiatal hernia in participants with BMI 20–25 was 1.9 with 95% CI 1.1–3.2, in those with BMI 25–30 was 2.5 with 95% CI 1.5–4.3, and in those with BMI 30–35 was 4.2 with CI 2.4–7.6 [18].

Pandolfino et al. specify that abdominal obesity when quantified by waist circumference is more indicative of risk for increased intra-abdominal pressure and hiatal hernia than BMI. Obesity causes increased intra-abdominal pressure, decreasing hiatal integrity, which increases risk for herniation. Greater BMI and waist circumference put added strain on the phrenoesophageal membrane, increase intra-abdominal pressure, and are associated with hiatal hernia [20].

Risk factors for paraesophageal hiatal hernia include thoracoabdominal trauma and having previous gastroesophageal surgery including antireflux procedures, esophagectomy, esophagomyotomy, or partial gastrectomy [18]. Skeletal deformities including scoliosis, kyphosis, and pectus excavatum predispose people to hernias due to distortion of diaphragmatic anatomy. Scoliosis is present in almost a third of patients with giant paraesophageal hernia [21]. Congenital defects are the most common cause of paraesophageal hernia in children; these are sometimes associated with other malformations, such as intestinal malrotation [22]. Metanalysis of the relationship between sex and hiatal hernia incidence determined it is more common among men with odds ratio 1.36, 95% CI 1.10–1.68, P = 0.005, and I 2 = 89.5 [18].

Symptoms

The most common symptom of hiatal hernia is gastroesophageal reflux, which is certainly not a specific finding. Hiatal hernia increases the incidence of strain-induced reflux, reduces the threshold for distention-induced transient lower esophageal sphincter relaxations, increases swallow induced reflux, reduces lower esophageal sphincter pressure, and impairs acid clearance. When the stomach has partially or completely herniated into the chest cavity, individuals are more prone to reflux as the lower esophageal sphincter and crus no longer work together to prevent gastric contents from re-entering the esophagus. Thus, heartburn and regurgitation are more likely to occur with intra-abdominal pressure spikes—coughing, straining, or bending over [19]. The supradiaphragmatic portion of the stomach often retains food and acidic fluid with the crus of the diaphragm acting as a waist that restricts emptying. Pressure and friction during respiration from the diaphragmatic crus on a partially herniated stomach can lead to gastric mucosal ulceration at the level of the hiatus. This was first postulated by Windsor and Collins in 1967 and later described by Cameron and Higgins in 1986 [23, 24]. Clinically relevant Cameron's lesions present with symptoms of anemia caused by upper gastrointestinal bleed—pallor, shortness of breath, melena, bloody vomitus, or fatigue.

Dysphagia more commonly accompanies paraesophageal hernia when the herniated portion of the stomach puts pressure on the distal esophagus as the lower esophageal sphincter has not migrated cephalad. Dyspnea is a worrisome symptom that tends to only present when a large portion of the stomach, or the entire stomach along with other organs—Type IV—has herniated into the thoracic cavity. Alarming symptoms with para-esophageal hernia include chest pain, epigastric pain, nausea, and vomiting; these may be harbingers of gastric ischemia or volvulus, the feared complications of this type of hernia [22, 25].

Diagnosis

Several imaging studies can assist in the diagnosis of hiatal hernia. Although many hiatal hernias are demonstrated incidentally on computed tomography—CT—studies for unrelated

reasons, a CT scan is not often a part of the normal diagnostic workup. When a patient presents with longstanding medically refractory symptoms of gastroesophageal reflux or the aforementioned alarm symptoms, further workup is warranted and can include upper endoscopy, barium swallow, and manometry [17, 22].

Endoscopy

Upper gastrointestinal endoscopy can diagnose hiatal hernia as well as visualize the stomach and esophagus for causes of bleeding, dysphagia, or pain. Endoscopy allows the operator to directly inspect the squamocolumnar junction and the constricting effect the hiatal opening normally has on the distal esophagus. A sliding hernia is diagnosed if the distance between these landmarks is greater than 2 cm [26, 27]. The esophagogastric junction can also be inspected via endoscopy by entering the stomach and then retroflexing. From this position, the shaft of the endoscope is visualized and the gastric entrance should be completely occluded by the scope. In a patient with hiatal hernia, there can be incomplete luminal closure around the endoscope as the hiatus has become lax, and the squamocolumnar junction can be displaced orad [28].

Endoscopic diagnosis of hiatal hernia has limitations. The esophagogastric junction is mobile in normal anatomy; it is pulled cephalad by peristalsis with contraction of the longitudinal layer of muscle in the wall of the esophagus, and can move during breathing or straining, but normal displacement does not exceed 2 cm. The examination itself can be confounding as excess insufflation of the stomach may exaggerate the size of a hiatal hernia, while instrumentation and insufflation of the esophagus can alter the apparent location of the squamocolumnar junction [27, 28]. Barrett's metaplasia or inflammation from significant reflux can also be confounding by obscuring the native squamocolumnar junction is obscured.

Barium Swallow

Hiatal hernia is often evident on plain films of the chest as a retrocardiac shadow; the anatomy can be demonstrated better with a barium swallow. The study provides information on the anatomical relationship of the stomach and esophagus, esophageal motility or stasis, esophageal stricture, gastric emptying, and limited information on masses or ulcers. This can also be of use as the images can be assessed for signs of achalasia. The nature of this study as a mechanical, mid-swallow evaluation makes the esophagogastric junction and its relation to the hiatus dynamic [22, 24].

Manometry and Reflux Monitoring

In patients who have been studied with manometry, as many as 30–60% had hypomotility, and more than 50% had hypotensive lower esophageal sphincter. In those with a large paraesophageal hernia, esophageal anatomy can be so distorted that manometry can be difficult and unhelpful. High resolution manometry can also identify the level of the crura of the diaphragm as well as the lower esophageal sphincter, but the dynamic nature of these structures make this measurement just as unreliable as other modalities. Reflux monitoring is also indicated when a hiatal hernia repair is being considered to control symptoms of gastroesophageal reflux. These studies assist in assessing peristalsis and the degree of reflux to plan the ideal type of fundoplication [22].

Classification

Hiatal hernias are described in four categories. Type I is the most common, accounting for over 85% of hiatal hernias, and is also called a "sliding hiatal hernia." In this pathology, the phrenoesophageal membrane has become circumferentially lax and the gastroesophageal junction migrates into the posterior mediastinum along with the stomach. In Type II hiatal hernia, the gastroesophageal junction remains in place, but there is a defect in a portion of the phrenoesophageal membrane through which the gastric fundus herniates. Type III hiatal hernias have elements of both gastroesophageal junction displacement and paraeophageal hernia pathophysiology. A Type IV hiatus hernia is a large defect

through which other organs such as the small intestine, colon, or spleen have herniated into the chest along with the stomach [29].

While gastroesophageal reflux disease is the hallmark of Type I hiatal hernias, Type II hernias are often asymptomatic until a significant portion of the stomach has herniated into the thoracic cavity and ischemia or obstruction ensue due to gastric volvulus. Regardless of hernia type, if reflux is occurring, surgical management may need to account for a foreshortened esophagus, which occurs in the setting of chronic inflammation and edema that leads to esophageal remodeling with scar [22, 29].

Candidates for Surgery

A type I or sliding hiatal hernia is not harmful in itself, so treatment is based on the symptoms of associated GERD and it does not necessitate surgical management. In patients with GERD refractory to maximum medical treatment or with whom the decision has been made to try to eliminate or reduce medical therapy due to side effects or concerns regarding long term medication use, a fundoplication operation is appropriate to address reflux disease and the hiatal hernia is repaired simultaneously [28]. Due to the risk of incarceration or strangulation in type II hernias and the risk of volvulus, venous congestion, ulceration, obstruction, and anemia in types III and IV, surgical treatment is favored with hiatal hernia repair. There are recent studies, including that by Stylopoulos, which suggest that watchful waiting is a reasonable alternative to operative management of asymptomatic hiatal hernia. The mortality from emergent repair of paraesophageal hernia on average is 17%, but has been reported as low as 0–5.4%. Stylopoulos also wrote in 2002 that the lifetime risk of developing acute symptoms with an asymptomatic hiatal hernia was 18% for a 65 year-old and decreased as the patient's age increased [30]. This data suggests that routine elective repair may not be indicated. Age should not be a barrier to symptomatic hernia repair, but the elderly with comorbidities or life expectancy less than 5 years may lose quality of life from an elective repair of an asymptomatic or minimally symptomatic hiatal hernia. In all cases, weight loss should be encouraged and respiratory status optimized for the lowest risk of adverse outcomes [31].

Surgical Strategy

Open transabdominal, open transthoracic, laparoscopic, and robotic-assisted approaches are acceptable techniques to undergo hiatal hernia repair. Thoracoscopic approaches are rarely used. The minimally invasive laparoscopic hiatal hernia repair is most commonly used, with the transthoracic approach reserved for patient with multiple prior transabdominal repair attempts or needing concomitant esophageal or pulmonary operation on the left side. Whether or not an anti-reflux operation and/or an esophageal lengthening procedure are required is controversial; some surgeons perform one or both of these procedures routinely, while others add them on a case-by-case basis depending on patient factors such as individual anatomy. A Collis-Belsey transthoracic approach serves as both esophageal lengthening and antireflux procedures and will be described below [32, 33]. Regardless of the methods utilized, the procedure of hiatal hernia repair has two generally accepted goals: mobilize the esophagus until there are at least 2.5 cm of tension-free intra-abdominal esophageal length and close the esophageal hiatus, which prevents reflux by recreating a zone of high pressure just before the esophagogastric junction.

Anesthesia and Positioning

After induction of general anesthesia, a double-lumen tube is placed for optimal lung isolation. The anesthesiologist also will assist with placement of the esophageal bougie or endoscope to aid proper sizing of the gastroplasty. It should be noted that an endoscope is smaller than the 52Fr or so bougie that is normally used to

approximate the desired size of the hiatus; this should be taken into account if using an endoscope. Prior to the incision, upper endoscopy can be performed to inspect for the presence of stricture, dysplasia, or other pathology prior to commencing the fundoplication and gastroplasty. In an emergent case, this should be done in the operating room to assess volvulus and for evidence of gastric necrosis; but the patient will likely have had this recently completed prior to elective surgical intervention. An epidural or paravertebral analgesic catheter is often beneficial. The patient should then be turned, propped, and secured with their right side down in position for left thoracotomy with pressure points padded appropriately. Flexing the operating table will open the rib interspaces to achieve maximal exposure [32, 33].

Collis-Belsey Transthoracic Fundoplication Gastroplasty

A postereolateral thoracotomy is created in the sixth or seventh rib interspace. As the pleural space is approached, the latissimus dorsi can be divided and the serratus anterior spared. The left inferior pulmonary ligament must be divided for adequate exposure of the esophagus. The hernia sac, if present, will be visible, and care must now be taken to identify the right and left vagus nerves. Once the esophagus is identified and freed from surrounding tissue, a Penrose drain can be passed behind it and used to retract it. The sac should then be dissected at the level of the hiatus circumferentially. Next, enter the abdomen by dividing the hernia sac and dissecting it away from the crura. The infradiaphragmatic stomach needs to be mobilized enough from surrounding tissue so that the herniated part of the stomach can be easily translocated below the diaphragm. Nonabsorbable sutures are placed across the crura both posterior and anterior to the esophagus approximately 1 cm apart to close the hiatus to a diameter of around 2.5 cm, but they are left untied until the end of the procedure. It is difficult to estimate the amount of intraabdominal esophageal length achieved during a transthoracic approach; therefore, typically a Collis gastroplasty is performed to guarantee adequate length, providing a neoesophagus around which to wrap so the wrap and stomach lie in the abdomen tension free. To perform the Collis, a 50–60Fr bougie or endoscope is advanced into the stomach, and a linear stapler is used vertically on the left and parallel to the bougie. If a cutting stapler is fired, the staple lines may be oversewn. The fundoplication procedure of choice can be completed at this time. We typically perform a Belsey-type fundoplication, during which three 2-0 silk interrupted mattress sutures are placed from the muscular esophagus to seromuscular bites of gastric fundus in a 270° wrap avoiding the anterior and posterior vagus nerves. A second row of three interrupted mattress sutures is then placed taking muscular esophageal bites 2 cm above the first set, seromuscular bites of stomach 2 cm below the first row, and finally incorporating the diaphragm to complete the fundoplication. Alternatively, a Nissen fundoplication can be completed by placing one or two mattress sutures that include the anterior stomach wall, then the muscular esophagus, and finally the posterior walls of the stomach to make a complete 360° wrap [34]. The anterior 180–200° Dor fundoplication or the 270° posterior Toupet fundoplication are all viable options for partial wraps in patient with esophageal motility issues prior to the operation. The crural sutures are tightened, and the hiatus inspected to ensure there is not significant tension on the repair and the stomach remains intra-abdominal. A nasogastric tube may inserted, if so desired, and placement is confirmed. Good lung expansion is visualized, and a standard chest drain is placed prior to closing the chest wall in standard fashion [32, 33].

Postoperative Management

A chest radiograph should be obtained in the recovery room to reassess the chest tube and nasogastric tube. Patients are cleared for prophylactic anticoagulation for deep venous

thrombosis prevention, and sequential compressive devices may be used on the lower extremities when in bed. The chest tube can be removed as early as the first day postoperatively if output is less than 200–300 ml without an air leak. The nasogastric tube, if used, may be removed per local protocol. Strict antiemetic precautions should be taken. A contrasted swallow study should be done to assess for leak and lower esophageal sphincter patency prior to advancing the diet. Patients should remain on a soft diet and avoid large pills, which can become impacted at the new esophagogastric junction. More solid food can be introduced after the postoperative visit provided that the patient is not experiencing dysphagia. The feared complication is leak at the gastroplasty site or esophageal tear leading to leak. Small leaks that are not accompanied by significant extraluminal fluid collections can be managed expectantly. In rare cases, operative exploration, drainage, and repair is required, which is best completed transabdominally if possible so the diaphragm repair can remain intact [35]. Persistent reflux should be worked up with a gastric emptying study to evaluated for delayed gastric emptying so a promotility agent can be prescribed. This will often ameliorate symptoms, and they may not need the medication long-term. If gastric motility is within normal limits, reflux symptoms can typically be subdued with medical management [36].

Conclusion

Symptomatic diaphragmatic relaxation can be surgically managed with a plication procedure completed via either transthoracic and transabdominal approaches, ideally with minimally invasive techniques. En bloc resection is the treatment of choice for diaphragmatic tumors, typically with mesh reconstruction of the diaphragm. Primary tumors are rare, with secondary tumors being most common. Sliding hiatal hernias should be managed based on the severity of associated symptoms—most often reflux—and surgical management only pursued if maximum medical therapy is unsuccessful. Although the majority of surgical management of symptomatic paraesophageal hernia is completed with the minimally invasive laparoscopic approach, the Collis-Belsey transthoracic approach remains an important consideration in patients who have had multiple prior transabdominal attempts at repair or patients requiring a simultaneous left-sided thoracic operation.

Exercises/Self-study

1. How can one best prevent phrenic nerve injury when performing a thoracoscopic diaphragmatic plication?
   (A) The phrenic nerves and vessels can be directly visualized from a thoracoscopic approach, so they can easily be avoided
   (B) The plication should only include the muscular diaphragm, avoiding the central tendon of the diaphragm
   (C) Bites through the muscular diaphragm should be taken relatively close to the central tendon, and the preoperative CT scan should be inspected to view the location of the phrenic nerve and vessels
   (D) A radial plication should be performed in all patients

   Explanation: Choice C is CORRECT. The right and left phrenic nerves pass through the diaphragm medially and provide branches to the muscular diaphragm. Unlike Choice B, the plication should either be completed radially or across the central tendon to minimize risk to the phrenic nerves. Choice A is incorrect because the course of the phrenic nerve branches cannot be visualized on the thoracic surface on the diaphragm. Unfortunately, a radial plication (Choice D) is not often feasible.
2. An patient with severe reflux disease is undergoing transthoracic Type III hiatal hernia repair. After circumferentially freeing the hernia sack and entering the abdomen, it is determined that there is 1 cm of intra-abdominal esophagus when tension-free. How should surgical management proceed?
   (A) Continue with a fundoplication, allowing the wrap to sit above the diaphragm
   (B) Form a neoesophagus by completing a gastroplasty and then proceed with

fundoplication, crural approximation, and closure

(C) Form a neoesophagus with a colonic interposition and then proceed with fundoplication, crural approximation, and closure

(D) No fundoplication should be completed, the hiatus should be closed with crural approximation sutures and the remainder of the procedure aborted.

Explanation: Choice B is CORRECT. A Collis gastroplasty can be performed to yield at least 2.5 cm of intra-abdominal esophagus so that a proper fundoplication can be performed as well as crural approximation. Choice A is incorrect because the fundoplication must sit below the diaphragm tension free or it will serve as a lead point for recurrence of the hernia. Choice C is not necessary, as the fundus of the stomach can be fashioned into a neoesophagus in the setting of non-neoplastic pathology. Choice D would not address the patient's severe reflux disease; a fundoplication is indicated in this patient.

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Management of Diaphragmatic Injuries

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Key Points

- The diaphragm is the principal muscle of inspiration. The function of each hemidiaphragm revolves around the dynamic generation of a tidal volume.
- The left diaphragm is affected in 75% of the cases as opposed to 25% on the right side, while bilateral TDI occur only in 2% of the patients.
- Clinical presentation may range from hemodynamic stability with few or no physical findings to severe hemodynamic compromise and/or presentation *in extremis* of patients with massive destruction of the thoracoabdominal region.
- Minimally invasive techniques such as laparoscopy and thoracoscopy are now part of the trauma surgeon's diagnostic armamentarium for both diagnosis and repair of TDI.
- Mortality from TDI is generally due to the associated injuries.

Introduction

The anatomo-physiologic structure and function of the diaphragm is responsible for the higher incidence of left-sided TDI. A congenital weakness along the embryonic fusion of the costal and lumbar portions of the diaphragm predisposes the left hemi-diaphragm to a greater incidence of injury from blunt trauma. In contrast, the presence of the liver along with its attachments underneath the right hemi-diaphragm accounts for the lower incidence of trans-diaphragmatic herniation following small defects from either penetrating or blunt trauma. In general, because of the significantly greater force required to cause right sided TDI, patients with injury to the right hemi-diaphragm have a higher pre-hospital mortality when compared to patients with left diaphragmatic injuries from associated severe hepatic and vascular injuries. The diagnosis of TDI requires a multimodality

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diagnostic approach. In fact, no single diagnostic study has been shown to be sufficiently sensitive and/or specific enough to accurately diagnose the presence of blunt or penetrating diaphragmatic injury. Minimally invasive procedures such as diagnostic laparoscopy and thoracoscopy are more commonly used to diagnose TDI in asymptomatic patients with penetrating trauma to the thoraco-abdominal region. The operative management of TDI depends on the clinical presentation of the patient and on the timeliness of the diagnosis. Patients with acute TDI typically undergo immediate open or laparoscopic operative management depending on the presence or absence of associated injuries. The objective of this chapter is to provide a concise approach to the diagnosis, surgical management, and treatment of diaphragmatic injury.

Physiology of the Diaphragm

The diaphragm is the principal muscle of inspiration. When the muscle is at rest, it presents a domed surface that is concave towards the abdomen. When the muscular fibers contract, they become less arched or nearly straight, causing the central tendon to descend. As a result, the level of the chest wall is lowered and the vertical diameter of the chest is proportionally increased. During this descent, the different parts of the tendon move unequally. The left leaflet descends to a greater extent than the right leaflet, primarily due to the liver, and the central leaflet descends the least because of its connection to the pericardium. In descending, the diaphragm compresses the abdominal viscera and causes an outward projection of the abdominal wall. However, because the central tendon becomes a fixed point, this enables the circumferential muscular fibers to contract and elevate the lower ribs thus expanding the lower part of the thoracic cavity. When at the end of inspiration the diaphragm relaxes, the thoracic wall return to its natural position as a consequence of its elastic recoil and of the elasticity and weight of the displaced viscera [1, 2].

In all acts in which expulsion of body fluids and/or solid materials, such as before vomiting, defecation, urination, and delivery of a fetus from a gravid uterus, and before sneezing, coughing, laughing, and crying, the diaphragm is called into action to give an additional power to the expulsive effort [1].

The height of the diaphragm varies during respiration as the muscle is carried upward and downward from the average level. Its height also varies according to the distention of the abdominal hollow viscera and the size of the liver. After a forced expiration, the right arch is on the level of the fourth costal cartilage; at the side, with the fifth, sixth, and seventh ribs; and behind, with the eight rib, the left arch being usually one to two ribs' breadth below the level of the right one. In a forced inspiration, it descends between one to two inches [1].

Pathophysiology of Diaphragmatic Injury

The function of each hemi-diaphragm revolves around the dynamic generation of a tidal volume. The generation of a normal tidal volume produces a 3–5 cm bidirectional trajectory of the diaphragm, with inferior displacement during inhalation and superior displacement during exhalation. During exhalation, the right hemi-diaphragm rises anteriorly to the level of the fourth intercostal space whereas the left hemi-diaphragm rises to the fifth intercostal space. Posteriorly, both hemi-diaphragm ascend to the eighth intercostal space. Constant diaphragmatic motion tends to preserve the negativity of the intrathoracic pressure, and during inhalation increases to its maximum.

As the main respiratory muscle of the body, the diaphragm has both inspiratory and expiratory functions. Changes in lung volume have a direct effect on diaphragmatic muscle fibers and their function. It is known that the transdiaphragmatic pressure from stimulation of the phrenic nerve decreases almost linearly with lung volume. This implies that the force-generating capacity of the diaphragm is reduced.

A close relationship also exists between the diaphragm and the musculature of the abdominal wall. These muscles also have both inspiratory and expiratory function. The abdominal wall muscles will contract during expiration, forcing the diaphragm cephalad into the thoracic cavity. Physiologic factors such as sudden and abrupt increases in the pleuroperitoneal pressure gradient have been identified as a pathogenetic mechanism of diaphragmatic injury. Marchand [3] demonstrated that there is a normal pattern of fluctuation in the intraperitoneal pressure during quiet respiration, which ranges from +2 cm to +10 cm of H_2O, while the corresponding intrapleural pressure fluctuates from −5 to −10 cm H_2O. With the body in the supine position, the pleuroperitoneal gradient fluctuates from +7 to +20 cm H_2O. With maximal inspiration, this gradient may exceed +100 cm of H_2O. Sudden increases in intra-abdominal pressure of +150 to 200 cm of H_2O are associated with the acute transfer of large amount of kinetic energy to the domes of the diaphragm, which in turn may cause diaphragmatic disruption.

If a violation of the anatomic integrity of the diaphragm occurs via laceration, perforation, or rupture, the pleuroperitoneal gradient will favor transdiaphragmatic migration and therefore herniation of intra-abdominal viscera [4]. Diaphragmatic disruption is associated with immediate hemodynamic and respiratory derangements. Transdiaphragmatic migration of herniating intra-abdominal viscera can restrict ventricular filling decreasing ventricular end-diastolic volumes, thereby reducing cardiac output. The displaced intra-abdominal viscera that migrate into the ipsilateral chest cavity can also compromise ventilation and may eventually compromise ventilation in the contralateral lung as the mediastinal shift increases.

Incidence and Injury Location

Diaphragmatic injuries occur infrequently in patients with both blunt and penetrating trauma. In a large review of the literature [5] that included 53,031 patients, a total of 592 patients were identified to have suffered with TDI, accounting for an overall incidence of 3% of all abdominal injuries. The mechanism of injury (MOI) of TDI depends on the reporting trauma center. Penetrating injuries predominate as the MOI in the inner-city and urban trauma centers, while blunt trauma is a much more common MOI of TDI in sub-urban and rural settings [6, 7]. The more widespread use of computed tomography particularly for the evaluation of blunt trauma patients has been associated with an overall relative increase in the incidence and detection of blunt traumatic diaphragm injuries [8].

Particularly in the setting of blunt trauma, left-sided hemi-diaphragmatic injuries are considerably more common than right-sided injuries. The incidence of left diaphragmatic was reported to be 75% as opposed to 25% right TDI, while bilateral diaphragm injuries were uncommon occurring only in 2% of the patients with TDI [9–11]. To elucidate the cause of the left-sided prevalence of diaphragmatic rupture, an study was performed in which 10 diaphragms were harvested from cadavers within the first 24 hours of death. Both the right and left hemi-diaphragm were mounted separately in a pressure chamber, and pressures were progressively increased until rupture of the hemi-diaphragm occurred. Although appeared that the right hemi-diaphragm required consistently higher pressures to rupture, the data did not reach statistical significance. Blunt left-sided injuries are usually located at the postero-lateral aspect of the hemi-diaphragm between the spleen and the abdominal aorta, and extend medially in a radial orientation towards the central tendon. Left-sided defects may present with herniation of the stomach, small bowel, colon, spleen, liver or omentum into the thoracic cavity.

Patients with right-sided hemidiaphragm rupture have higher pre-hospital mortality resulting from the greater impacting force required to produce a right-sided TDI, with such greater force typically associated with significant vascular tears in the inferior vena cava or hepatic veins. The apparent low incidence of right-sided TDI has been attributed to the cushioning effect of

the liver and to the greater force required to rupture the right hemi-diaphragm. It has been postulated that diaphragmatic injuries result from the transmission of force through the abdominal viscera to the diaphragm, resulting in rupture. This would explain the common involvement of the left hemi-diaphragm, which is unprotected as compared to the right. The energy from the force applied to the abdomen or flank should be distributed equally in all directions throughout the abdominal visceral contents.

Mechanisms of Injury

Penetrating injuries occur due to gunshot wounds, stab wounds, and shotgun wounds, whereas blunt injuries result from motor vehicle collisions, falls from heights or direct impacts to the thoracoabdominal area from vehicles (as is in the case of pedestrians being struck by vehicles). Blunt force trauma to the thoracoabdominal region or a history of crush injury should also alert the trauma surgeon to the possibility of an underlying diaphragmatic injury. A recent review of the National Trauma Data Bank (NTDB) revealed that patients with blunt traumatic diaphragmatic injuries are older and have a higher injury severity score (ISS) [12].

Associated Injuries

The diaphragm, because of its anatomic and its dynamic function, is rarely injured in isolation; in fact, the presence of associated injuries is the rule rather than the exception. The pattern of associated injuries generally depends on the mechanism of diaphragmatic injury (i.e., blunt versus penetrating, crush versus fall, etc.). Blunt trauma generally produces a significant number of extra-abdominal and/or extrathoracic injuries. The presence of diaphragmatic injury in the setting of blunt trauma should alert the physician to the high probability of associated solid organ and pelvic injury.

Clinical Presentation

In patients involved in MVC, information about the velocity of impact, the severity of vehicular damage, where the patient was found within the vehicle, and the direction of impact are all important in assessing the severity of the injury. Additionally, the presence or absence of passenger-compartment intrusion, the use and type of safety restraints, deformity of the steering wheel, and the duration and type of extrication required to retrieve the victim are also useful in understanding the impact to the patient and can help the treating physician assess possible associated injuries.

Falls from great heights, direct impacts on the thoracoabdominal area from vehicles, or a history of crush injury should also alert the trauma surgeon to the possibility of an underlying diaphragmatic injury. In general, the severity of other associated injuries may distract the attention of the trauma surgeon and compromise the ability to identify the presence of diaphragmatic injuries.

While blunt trauma generally produces no external signs that are pathognomonic for TDI, penetrating trauma in the thoracoabdominal area immediately alerts the trauma surgeon to the possibility of diaphragmatic injury. The thoracoabdominal region consists of the lower chest and upper abdomen. It is divided into the following: the anterior thoracoabdominal zone, defined as the area between the nipples superiorly and the costal margin inferiorly; the lateral component, defined superiorly by a line drawn from the anterior axillary line at the level of the nipples posteriorly to the tip of the scapula and inferiorly to the costal margin; and the posterior thoracoabdominal area, defined anteriorly by a line at the level of the tips of the scapula and inferiorly by a line beginning at the posterior axillary line at the level of the inferior most ribs. In general, the incidence of diaphragmatic injury is approximatively the same for penetrating injuries to the three thoracoabdominal areas [13].

Presentation may range from hemodynamic stability with few or no physical findings to

severe hemodynamic compromise and/or presentation *in extremis* of patients with massive destruction of the thoracoabdominal region from close-range shotgun injuries (less than 3 yards or 2.7 meters). In the majority of patients, there are no signs or symptoms directly attributable to the diaphragmatic defect. Symptoms and signs attributable to TDI include shoulder and/or epigastric pain, respiratory distress, and the presence of obvious bowel sounds in the involved hemithorax.

Diagnosis and Imaging Studies

The diagnosis of a diaphragmatic injury presents a challenge to the trauma surgeon, as evidenced by the large number of investigative procedures employed to arrive to the diagnosis. Injuries to the diaphragm may be identified non-invasively with radiological studies and/or invasively with interventional diagnostic procedures. The initial test of choice is a chest X-ray, which can be diagnostic when hollow abdominal viscera or a nasogastric tube is/are detected in the hemithorax. The treating physician must be aware that on the initial films, diaphragmatic rupture may present as atelectasis, hemothorax, pneumothorax, gastric dilatation, pulmonary contusion, intra-abdominal fluid, traumatic pneumatocele or congenital eventration.

Occasionally, in acute ruptures of the left hemidiaphragm, the nasogastric or orogastric tube placed during the resuscitative phase can be found coiled in the left hemithoracic cavity (Fig. 1). Other findings occasionally

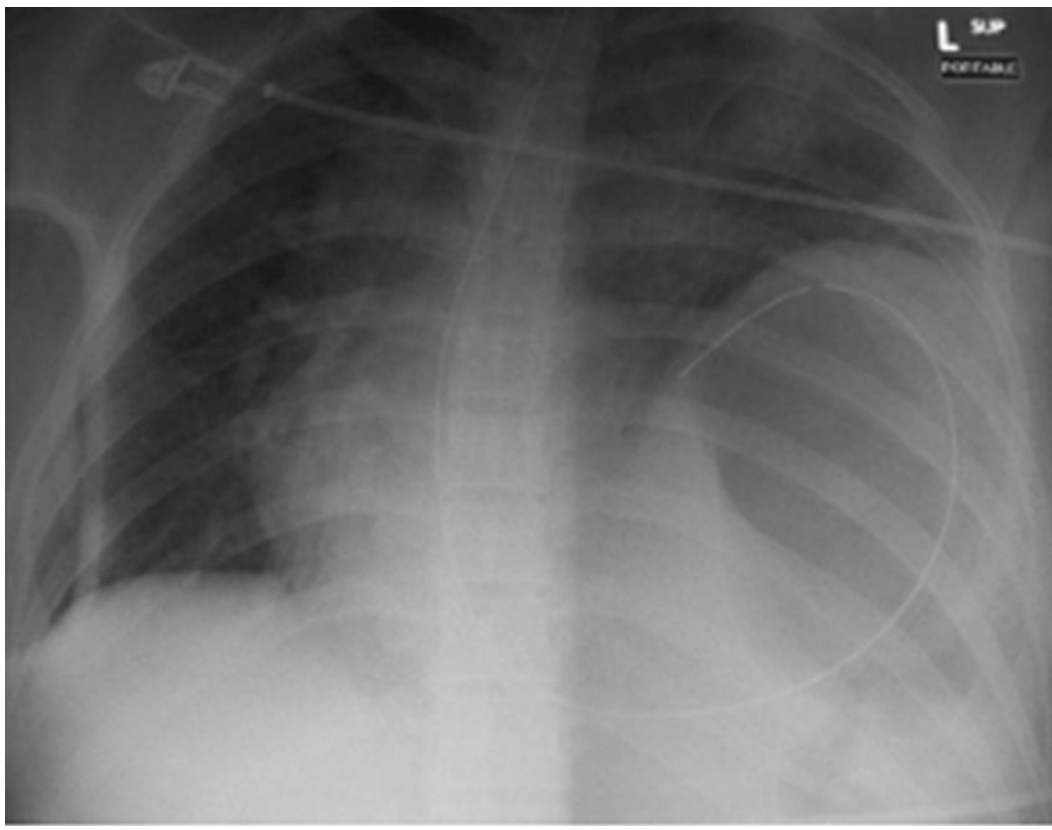

Fig. 1 A coiled nasogastric tube within the left hemithoracic cavity is pathognomonic for a rupture of the left hemidiaphragm (with permission from Dr. Petrone's personal archives)

identified radiographically are curvilinear shadows and air-fluid levels consistent with hollow viscera, such as colon or small bowel in the intra-thoracic space. These findings are pathognomonic for rupture of the diaphragm.

Computed tomography (CT) has become readily available in the assessment of the acutely injured patient. Currently, reconstructed images are routinely obtained in patients with chest radiographic findings suspicious of TDI, namely an abnormally elevated hemi-diaphragm. The use of multi-detector computed tomography (MDCT) with coronal and sagittal multiplanar reformation (MPR) has improved the accuracy of CT for the diagnosis of TDI.

Minimally invasive techniques such as laparoscopy and thoracoscopy are also part of the trauma surgeon's diagnostic armamentarium. Laparoscopy has been shown to be extremely useful to detect diaphragmatic injury in patients who have no other indications for laparotomy. Hemodynamically stable patients without abdominal symptoms with left thoracoabdominal penetrating trauma should undergo diagnostic laparoscopy for the diagnosis and repair of diaphragmatic injury from penetrating trauma [14, 15].

Although thoracoscopy is used s less frequently than laparoscopy, it has been shown to have a high sensitivity and specificity with an accuracy rate of 98–100% for the diagnosis of diaphragmatic injury in stable patients. Its main disadvantages include the amount of time it takes to place the patient in a thoracotomy position, it does not always allow repair of the diaphragm, and it always requires chest tube insertion even if negative. In addition, in the acute setting and with concerns for intra-abdominal injury, thoracoscopy is limited. These seem to be the reported reasons why thoracoscopy is used less frequently than laparoscopy. It is our opinion that the choice of laparoscopy or thoracoscopy for the diagnosis and treatment of diaphragmatic injury in the setting of penetrating trauma to the thoracoabdominal region depends on the familiarity and comfort level of the individual trauma surgeon with each modality [14, 16].

Surgical Management of Diaphragmatic Injuries

In patients suspected of having TDI, special attention must be paid to avoiding low placement of thoracostomy tubes, particularly if the CXR is suggestive of the presence of herniated viscera into the chest.

The majority of TDIs can be approached through a standard laparotomy. Full visualization of the diaphragm is required; exposure of the right hemi-diaphragm requires transection of the falciform ligament, whereas visualization of the left hemi-diaphragm requires gentle downward retraction of the spleen and greater curvature of the stomach, along with the central tendon of the diaphragm and the esophageal hiatus [17].

All herniated viscera must be reduced, with relocation to the original abdominal positions. After careful reduction and relocation of all herniated viscera, debridement should be undertaken of any devitalized diaphragmatic tissue. The defect is repaired with non-absorbable suture and an ipsilateral tube thoracostomy is usually performed under direct visualization. Diaphragmatic lacerations smaller than 5 cm should be repaired with non-absorbable suture, in vertical mattress fashion placed at approximately 1 cm from the edges, everting the diaphragmatic muscle toward the abdomen. In the cases of lacerations larger than 5 cm, we favor repair with a running interlocking suture with a non-absorbable suture, such as polypropylene. A diaphragmatic injury identified during

Table 1 American Association for the Surgery of Trauma-Organ Injury Scale (AAST-OIS) for Diaphragmatic Injuries [18]

Grade	Injury description
I	Contusion
II	Laceration ≤2 cm
III	Laceration 2–10 cm
IV	Laceration >10 cm with tissue loss ≤25 cm^2
V	Laceration with tissue loss >25 cm^2

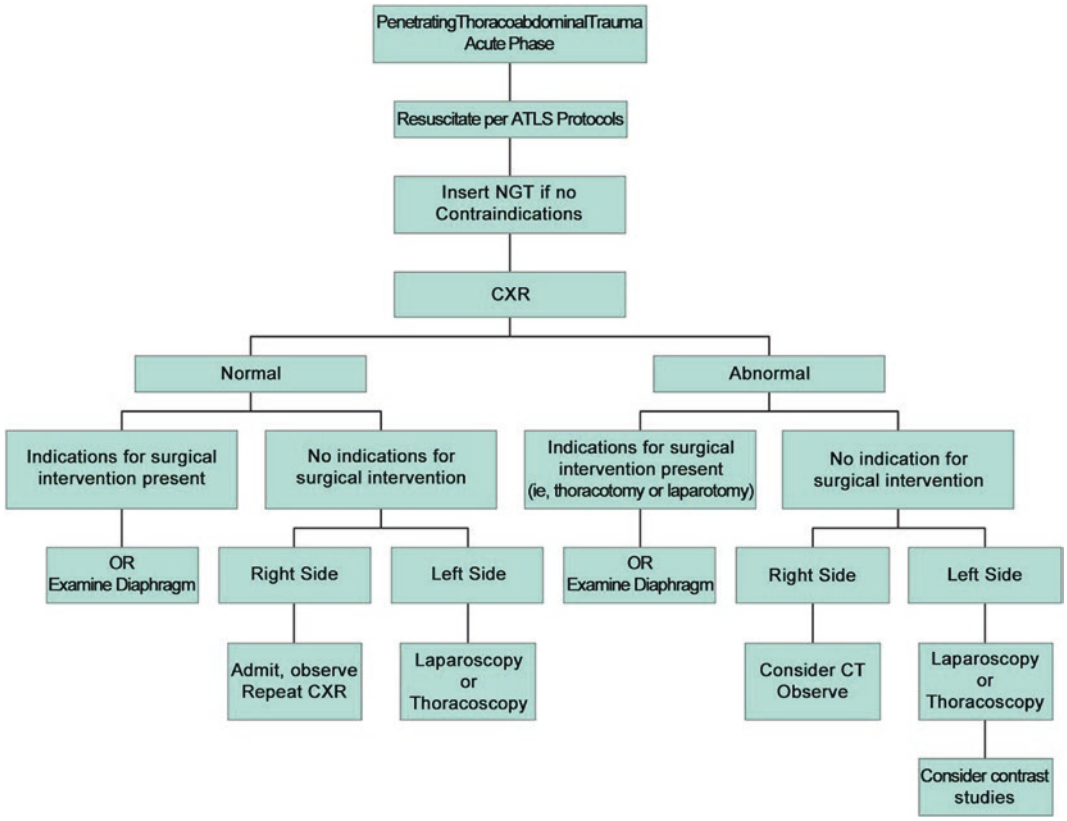

Fig. 2 Algorithm for penetrating thoracoabdominal trauma. ATLS, Advanced Trauma Life Support; CT, computed tomography; CXR, chest radiograph; OR, operating room; NGT, nasogastric tube (adapted and reproduced with permission from Asensio, Petrone and Demetriades [5])

laparoscopy or thoracoscopy may be repaired The anesthesiologist produces a forceful insufflation of the lung and the catheter is removed while simultaneously placing the final stitch in the diaphragm, The integrity of the diaphragmatic repair should be confirmed by having the anesthesiologist inflate the lung with large tidal volumes (15 ml/kg) followed by a Valsalva maneuver while the upper abdominal compartments are flooded with sterile saline [5].

Diaphragmatic lacerations smaller than 5 cm should be repaired with non-absorbable material, in vertical mattress fashion placed at approximately 1 cm from the edges, everting the diaphragmatic muscle. In the cases of lacerations larger than 5 cm we favor repair with a running interlocking suture with a non-absorbable suture, such as Prolene. A diaphragmatic injury identified during laparoscopy or thoracoscopy may be repaired laparoscopically or thoracoscopically as well.

Patients with TDIs associated with massive contamination of the pleural space from enteric content should undergo anterolateral thoracotomy followed by copious lavage to evacuate the contaminating material and placement of a 28 F right angle and 36 F straight chest tubes to drain the chest cavity and allow resorption of the pneumothorax, respectively. Penetration of the pericardial cavity with contamination requires lavage, keeping the pericardium open and placement of a pericardial drain.

While repair of acute TDIs can be accomplished through a thoracotomy, we believe that the trans-abdominal approach offers advantages over the thoracotomy approach with respect to

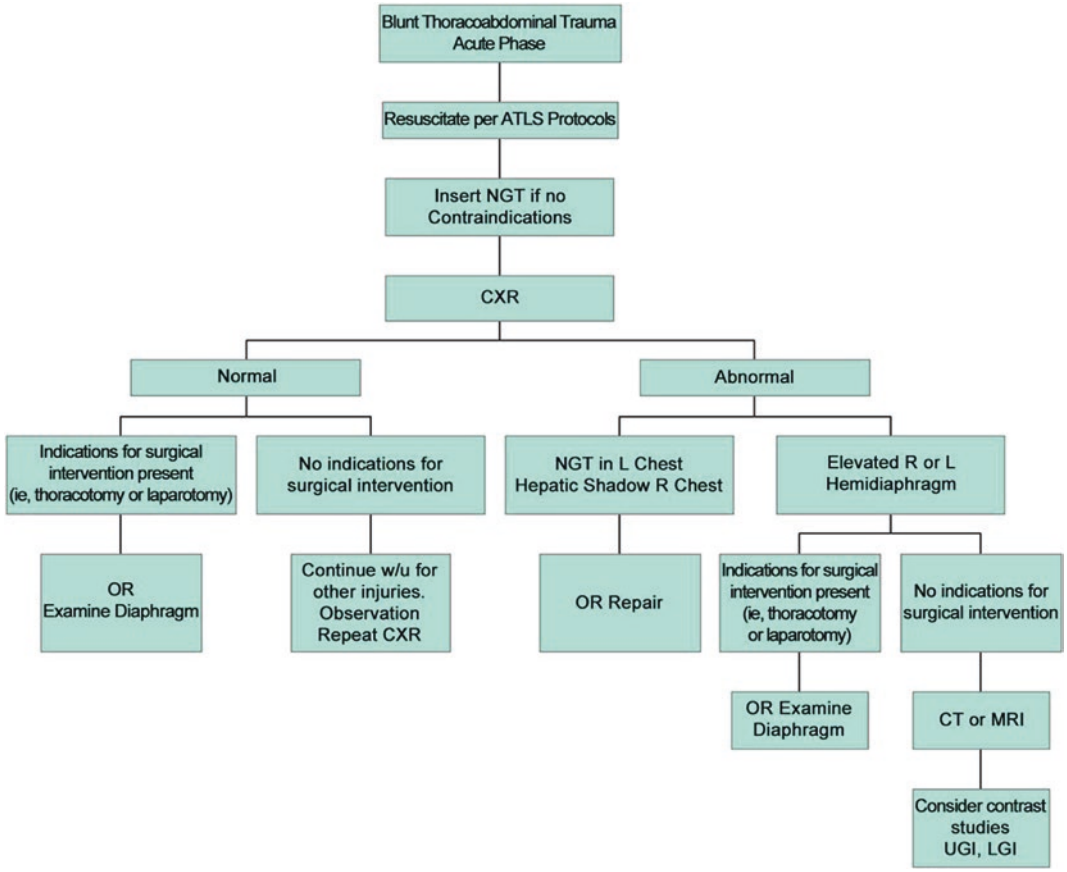

Fig. 3 Algorithm for blunt thoracoabdominal trauma. ATLS, Advanced Trauma Life Support; CT, computed tomography; CXR, chest radiograph; LGT, lower gastrointestinal; MRI, magnetic resonance imaging; NGT, nasogastric tube; OR, operating room; UGT, upper gastrointestinal (adapted and reproduced with permission from Asensio, Petrone and Demetriades [5])

the ease of reduction of herniated intra-abdominal viscera and with respect to the avoidance of missed intra-abdominal injuries.

Massive destruction of the diaphragm and chest wall can be caused from close-range (less than 3 yards) shotgun wounds. Patients who survive these devastating injuries present the operating surgeon with technical challenges that require complex reconstruction of the diaphragm and chest wall sometimes with staged procedures. Immediate reconstruction of the chest wall in patients with limited injury to the diaphragm that allows its use as a rotation flap can be accomplished by detaching the affected hemi-diaphragm from its anterior, lateral, and posterior attachments and by translocating it to a position above the chest wall defect. Following the repositioning of the diaphragm, by suturing it to the muscles at a higher level of intercostal space, the newly created abdominal wall defect can be repaired with a latissimus myo-cutaneous flap. Prosthetic non-absorbable mesh material can also be used to reconstruct the diaphragm, but its use is contra-indicated in the presence of contamination in either or both cavities, because of the associated risks of infection.

The authors recommend using the American Association for the Surgery of Trauma Organ Injury Scale (AAST-OIS) to grade

TDIs (Table 1) [18], as it has value as both a descriptive and research tool. Shown in Figs. 2 and 3 are the management algorithms for both penetrating and blunt thoracoabdominal trauma.

Morbidity and Mortality

The morbidity associated with traumatic diaphragmatic injuries can be subdivided into the morbidity attributable to the injury itself and the morbidity resulting from the surgical procedure required to repair the injury. The surgical morbidity includes suture-line dehiscence, and hemidiaphragmatic paralysis secondary to iatrogenic phrenic nerve injuries. The morbidity directly attributable to the injury itself includes respiratory insufficiency, and the development of empyema and sub-phrenic abscess. The morbidity associated with the missed diagnosis of TDIs includes respiratory compromise, most often secondary to atelectasis of the ipsilateral lung, pneumonia, bowel obstruction, strangulation and occasionally, perforation of herniated intra-abdominal viscera.

Mortality from diaphragmatic injuries is generally due to the associated injuries, and it can be as high as 51% in patients with four or more associated injuries and shock lasting longer than 30 minutes. The mortality rates are higher in series reporting TDIs from blunt diaphragmatic injuries reporting mortality rates of 27% and higher, as opposed to series of patients with TDIs from penetrating trauma, that report an average mortality of only 5%.

Self-study

1. Which diaphragmatic leaflet/s is/are most frequent affected?
   a. Right side
   b. Left side
   c. Bilateral
2. Which statement is true?
   a. There are not physical findings most of the time.
   b. MRI is the imaging study of choice to arrive to the diagnosis.
   c. Mortality from diaphragmatic injuries is generally due to the associated injuries.

Correct answers
Question 1: Answer b.
Question 2: Answer c.

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Post-traumatic Diaphragmatic Hernias

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Key Points

- The diaphragm is a dome-like muscular and tendinous septum. It separates the thoracic from the abdominal cavity in a dynamic volumetric fashion.
- It has three major openings: the aortic hiatus, the aorta, azygos vein, and thoracic duct pass through this opening; the esophageal hiatus, esophagus and vagus nerves; and the vena cava hiatus, for the vena cava only.
- Clinical presentation depends on the size of the defect, the content of the hernia, the type of the herniated organ/s and to whether the herniated organ/s is obstructed or ischemic.
- Chronic diaphragmatic hernias from missed traumatic diaphragmatic injuries (TDI) can be approached through the chest or abdomen with the choice depending on the clinical presentation and the surgeon's skill or preference.

Introduction

Accurate diagnosis of a traumatic diaphragmatic injury (TDI) is critical. A missed TDI may result in grave sequelae due to herniation and strangulation of displaced intra-abdominal organs, and respiratory compromise. TDI can result from blunt and penetrating trauma, and less commonly can be iatrogenic. The mechanism of injury (MOI) plays a significant role in the probability of a patient succumbing to a TDI. Therefore, the physician taking care of the trauma victim should inquire about the specifics of the MOI in order to minimize the chance of missing an injury.

The operative management of chronic TDI depends on the timeliness of the diagnosis. Patients with missed TDI typically undergo repair via thoracotomy. It is clear that missed injuries or delayed diagnosis portend a poorer prognosis. The purpose of this chapter is to review the anatomy of the diaphragm as it relates to traumatic injuries, and to provide a concise approach to their diagnosis, surgical

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management, and treatment of chronic diaphragmatic injuries.

Anatomy

The diaphragm is a dome-like muscle with a tendinous septum originating from the sternum, the ribs, and the 12th thoracic and first, second, and third lumbar vertebrae. It is the most important inspiratory muscle, and unlike skeletal muscles is constantly active. Its' location allows for the separation of the thoracic from the abdominal cavity in a dynamic volumetric fashion due to its position in inspiration as opposed to expiration. When relaxed and viewed from below, it forms a dome-shaped roof for the abdomen. The undersurface of the diaphragm covers the liver, intra-abdominal portion of the esophagus, stomach, spleen, adrenals, and kidneys, and to some extent the pancreas and transverse colon. Clearly, the severity of injury and the consequent surgical challenges to the management of diaphragmatic rupture increase dramatically depending on the associated intra-abdominal injuries [1].

The diaphragm provides a musculo-fibrous floor for the thorax. The peripheral muscular portions of the diaphragm arise from the lower six ribs and costal cartilages, from the lumbar vertebrae (right and left crus), and from the lumbo-costal arches. The most anterior portion of the diaphragm attaches to the lowermost aspect of the sternum at the posterior aspect of the xyphisternal junction, while the most posterior portion inserts in the periosteal surfaces of the first through the third lumbar vertebral bodies. The broadest portion of the diaphragmatic muscle spans laterally and attaches to the internal surfaces of the lower ribs. This lateral insertion extends from the sixth rib anteriorly to the twelfth rib posteriorly. Additional fibers arise from the xiphoid cartilages. All the muscular elements converge into the central tendon, roughly trifoliate in outline, and is the strongest and thinnest part of the structure. The central part of the tendon underlies the pericardium, while the right and left divisions extend posteriorly [1, 2].

Of the three major openings in the diaphragm, the aortic hiatus is the most posterior. It is situated slightly to the left of the midline, immediately in front of the body of the first lumbar vertebra, and is, therefore, behind the diaphragm, not in it. Precise knowledge of this anatomy allows the trauma surgeon to locate the abdominal aorta in order to compress it, either digitally or with the help of a long aortic cross-clamp during episodes of hypotension and exsanguinating abdominal vascular hemorrhage. The aorta, azygos vein, and thoracic duct also course through this opening. The esophageal hiatus is limited to the transition of the esophagus and vagus nerves from the thoracic to the abdominal cavity. The inferior vena cava courses as a single structure through a dedicated foramen, named vena cava hiatus, also known as the quadrate hiatus, and lies 1.5–2 cm to the right of the midline. The splanchnic nerves and sympathetic chains pass through two small foramina in the crura. The internal mammary arteries with anterior lymphatic trunks transit through a space between the sternal and costal portions of the diaphragmatic Morgagni's foramen, where congenital hernias may develop [1, 2].

In relation to the diaphragm, there are four serous membranes: three lining its upper or thoracic surface, and one lining its abdominal surface. The three serous membranes on its upper surface are the pleura on each side and the serous layer of the pericardium, which covers the middle portion of the tendinous portions of the diaphragm. The serous membrane covering the abdominal surface is a portion of the general peritoneal membrane of the abdominal cavity [2, 3].

The diaphragm is innervated by the phrenic nerves. The right and left hemidiaphragm are innervated separately by their respective ipsilateral phrenic nerves. The phrenic nerves arise from the third through the fifth cervical roots, with the greatest contribution to diaphragmatic innervation being consistently from the fourth cervical root. These nerves course anteriorly on

the medial border of the scalenus anticus muscle and traverse the thoracic cavity, traveling along the posterolateral mediastinum on the pericardial surface. The phrenic nerves typically divide into branches, either at the level of the diaphragm or 1–2 cm immediately above it. Some of the lower intercostal nerves are thought to contribute to the sensory innervation of the diaphragm, but motor innervation is supplied exclusively by the phrenic nerve on each side [2]. Each branch divides into four major rami: a sternal (anterior), an anterolateral, a posterolateral, and a crural (posterior) ramus. The resulting pattern is best described as a double "handcuff," with the anterolateral and posterolateral branches being the main components skirting circumferentially and laterally to the dome of the diaphragm.

Embryologic Development

The diaphragm has a highly complex origin. The classic concept of formation suggests that the diaphragm originates from the septum transversum, the mesentery of the esophagus, the pleuroperitoneal membranes, and the musculature of the chest wall. There are two paired (pleuroperitoneal membranes, chest wall musculature) and two unpaired (septum transversum, mesentery) components.

The septum transversum develops during the fourth week of gestation and initially appears as a thick, incomplete partition between the pericardial and peritoneal cavities. Originally, the septum is located opposite to the cervical vertebrae, but as it develops it becomes displaced caudally to reach the level of the first lumbar vertebra. Eventually, it fuses dorsally with the ventral mesentery to the esophagus and with the pleuroperitoneal membranes. In the adult, the septum transversum forms the central tendon of the diaphragm. The dorsal mesentery of the esophagus also appears during the fourth week of gestation and constitutes the median portion of the diaphragm dorsal to the septum transversum. In the adult, this mesentery forms the crura of the diaphragm, including the esophageal hiatus and aortic hiatus. During the fifth week of gestation, the pleuroperitoneal membranes first appear along the lateral body wall and extend medially, where they fuse with the dorsal mesentery of the esophagus and the dorsal portion of the septum transversum, completing the partition between the thoracic and abdominal cavities by the eighth week of gestation. Although the pleuroperitoneal membranes may form large portions of the primitive diaphragm, they represent relatively small intermediate portions of the adult diaphragm. Finally, with further development of the lung, the pleural cavities enlarge and burrow into the lateral body walls where the chest wall musculature is split off, forming the peripheral muscular portion of the diaphragm. Failure of any component to fuse with adjacent structures may result in congenital continuity of the pleural and peritoneal cavities [3, 4].

Initially, the septum transversum lies opposite the cervical somites, and nerve components of the third, fourth, and fifth cervical segments of the spinal cord into the septum. At first, the nerves known as the phrenic nerves, pass to the septum through the pleuropericardial folds. This explains why, with the further expansion of the lungs and descent of the septum, they are located in the fibrous pericardium. Hence, in the adult the phrenic nerves reach the diaphragm via the fibrous pericardium [4].

Although the septum transversum lies opposite the cervical segments during the fourth week, by the sixth week the developing diaphragm is located at the level of the thoracic somites. This descent of the diaphragm is apparently caused by rapid growth of the dorsal part of the embryo in comparison to the ventral part. By the beginning of the third month, some of the dorsal bands of the diaphragm originate at the level of the first lumbar vertebra [4].

The phrenic nerves supply the diaphragm with its motor and sensory innervation. Since the most peripheral part of the diaphragm is derived from mesenchyme of the thoracic wall, it is generally accepted that some of the lower intercostal nerves contribute sensory fibers to the peripheral part of the diaphragm [3, 4].

Because the diaphragm is formed from the fusion of several components, a number of developmental defects may occur, including complete absence of the diaphragm, diaphragmatic hernias (posterolateral or Bochdalek, anterior or Morgagni, and paraesophageal), and eventration. These abnormalities are not the scope of this chapter as the focus is diaphragmatic hernia as result of trauma.

Mechanism and Location of Injury

Penetrating injuries predominate as the mechanism of injury (MOI) in both the inner-city and urban trauma centers, while blunt trauma is a much more common MOI of traumatic diaphragmatic injuries (TDI) in both sub-urban and rural settings [5, 6]. The more widespread use of computed tomography particularly for the evaluation of blunt trauma patients has been associated with an overall relative increase in the incidence and detection of blunt traumatic diaphragm injuries [7].

Left-sided hemi-diaphragmatic injuries are considerably more common than right-sided injuries. The incidence of left hemi-diaphragmatic injuries was reported to be 75% as opposed to 25% right TDI, while bilateral diaphragm injuries were uncommon occurring only in 2% of the patients with TDI [8–10].

Clinical Presentation

In patients with delayed presentation and chronic herniation, symptoms of partial or complete intestinal obstruction may be present. When this occurs as a result of an incarcerated intrathoracic segment of bowel, the physical examinations findings depend on the anatomic level of obstruction. Gibson [11] stressed the importance of clinical signs in establishing the diagnosis of diaphragmatic hernia. He cited the following diagnostic symptoms:

- Diminished expansion of the chest
- Impairment of resonance
- Adventitious sounds
- Cardiac displacement
- Circulatory collapse
- Cyanosis and dyspnea
- Asymmetry of hypochondria

Generally, symptoms attributable to the presence of a diaphragmatic hernia depend on the size of the defect, the content of the hernia, the type of the herniated organ/s and whether the herniated organ/s are incarcerated causing obstruction or strangulation leading to ischemic perforation. Thoracic symptomatology is related to the volume of the pleural space occupied by the displaced abdominal viscera. Dyspnea, orthopnea, and chest pain are the primary symptoms. The latter may be diaphragmatic and be referred to the scapular area, or may be related to chest wall injury or pleural violation. In the event of progressive gastric dilatation, respiratory distress may become so extreme due to lung collapse that it may mimic the presence of tension pneumothorax. Physical findings include decreased breath sounds and multiple associated rib fractures. Abdominal symptoms tend to be less pronounced ranging from mild and localized to diffuse abdominal tenderness.

Diagnosis and Imaging Studies

Contrast studies are valuable in cases where the initial Chest X-Ray (CXR) is suspicious but has failed to yield a definitive diagnosis of TDI. Clearly, the patient must be hemodynamically stable in order to undergo these studies. In general, the vast majority of such studies are done to investigate chronic, longstanding herniation of intra-abdominal viscera, although they have also proven to be valuable in the acute settings. An upper gastrointestinal series and a barium enema will often delineate the presence of the stomach or colon within the thoracic cavity (Fig. 1a, b) [12]. Although not generally considered helpful, real time ultrasonography (US) may occasionally reveal a diaphragmatic rupture in expert hands. Despite the advent of the Focused Abdominal Sonography

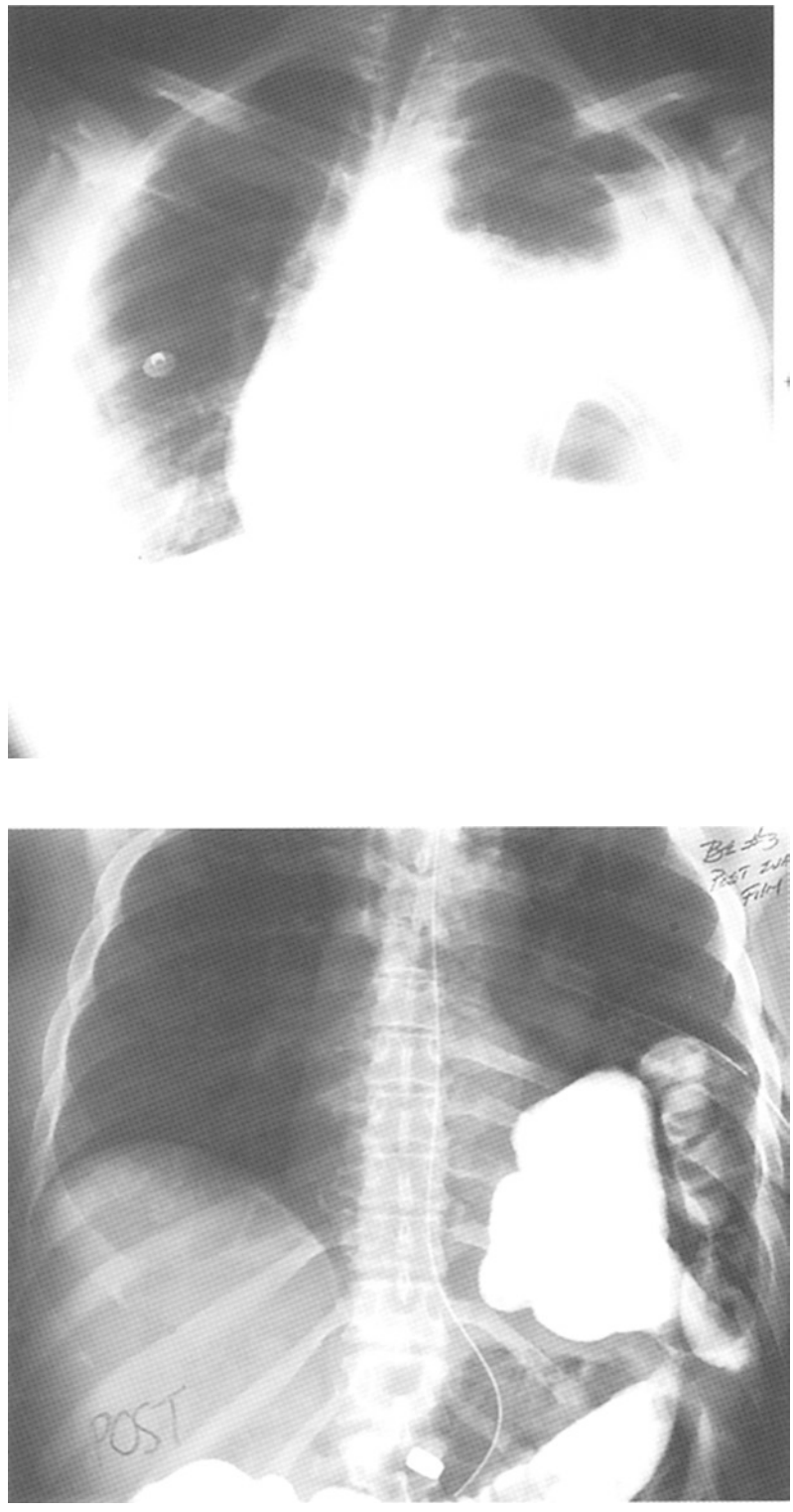

Fig. 1 **a** An intra-abdominal viscera (colon) migrated to the left chest (from Dr. Petrone's personal archive). **b** A barium enema delineates the presence of the colon within the thoracic cavity (from Dr. Petrone's personal archive)

for Trauma (FAST) as an accurate technique for the diagnosis of intra-abdominal or pericardial fluid in trauma patients, no definitive reports have emerged describing its usefulness for the diagnosis of TDI. The use of magnetic resonance imaging (MRI) has been reported to describe its use to assess the integrity of both hemidiaphragms.

Delayed Diagnosis and Missed TDI

Patients with a missed diagnosis of TDI typically will have a clinical course over time (months to years), characterized by progressive increase in visceral herniation, and the development of symptoms and signs of cardiorespiratory compromise. Obstruction, and occasionally strangulation with perforation of the segment of the herniated gastrointestinal tract into the involved hemithorax can occur [13–15].

The diaphragm as a muscle, tends to retract rapidly and it undergoes significant atrophy over time. As a result, and while its repair by re-approximating the edges of the defect can be accomplished easily on the day of injury, the primary repair of a missed TDI is much more difficult due to the presence of herniated viscera and atrophy from retraction of the muscle. Due to the changes that occur over time in the diaphragm of patients with missed TDI, primary repair is associated with a high rate of suture line failure, therefore, it is preferable to use alternate techniques to repair chronic TDI, including the use of prosthetic material to repair the defect [16]. Figure 2 shows the algorithm for the treatment of patients with delayed diagnosis of TDI from blunt and penetrating trauma [17].

Feliciano [18] reported 16 patients who had a delay in diagnosis of diaphragmatic injuries secondary to penetrating trauma; of note, three of them had diaphragmatic injuries missed at the time of laparotomy. Walschmidt [19] in 1968 reported a patient who underwent a successful reduction of a traumatic diaphragmatic injury and repair 41 years after a blunt injury; this case report involves the longest delay between time of the TDI and its treatment.

Surgical Management

The repair of acute diaphragmatic injury is best accomplished via exploratory laparotomy, while diaphragmatic injuries diagnosed on a delayed basis are more safely treated and repaired through a thoracotomy. In an extensive review of the literature [13], 27 series were analyzed totaling 1,530 patients with the diagnosis of TDI. Of the 1,530 reported TDIs, 1,133 (74%) were repaired via laparotomy, 371 (24%) via thoracotomy, and 119 required a thoracoabdominal approach via either a single incision extended from the abdomen to the chest or through two distinct incisions.

Laparoscopy may be the preferred surgical approach over open repair in those patients with isolated TDI who are hemodynamically stable. It is also superior in diagnostic capability to CT in most patients needing evaluation for penetrating TDI. Robotic surgery in this group of patients may be a viable option in expert hands. The abdominal approach will dominate over the thoracic approach in case where the life-threatening nature of associated injuries is the scenario. Chronic diaphragmatic hernias from missed TDI can be approached through the chest or abdomen and the choice of approach will depend on the acuity of presentation (emergent vs. elective), concern for difficulties reducing the hernia back into the abdomen, and surgical specialization of the surgeon [20].

Special Situations

Strangulated Diaphragmatic Hernias

Gastrointestinal incarceration and strangulation are the most serious complications of diaphragmatic hernias. Carter [21] defined the

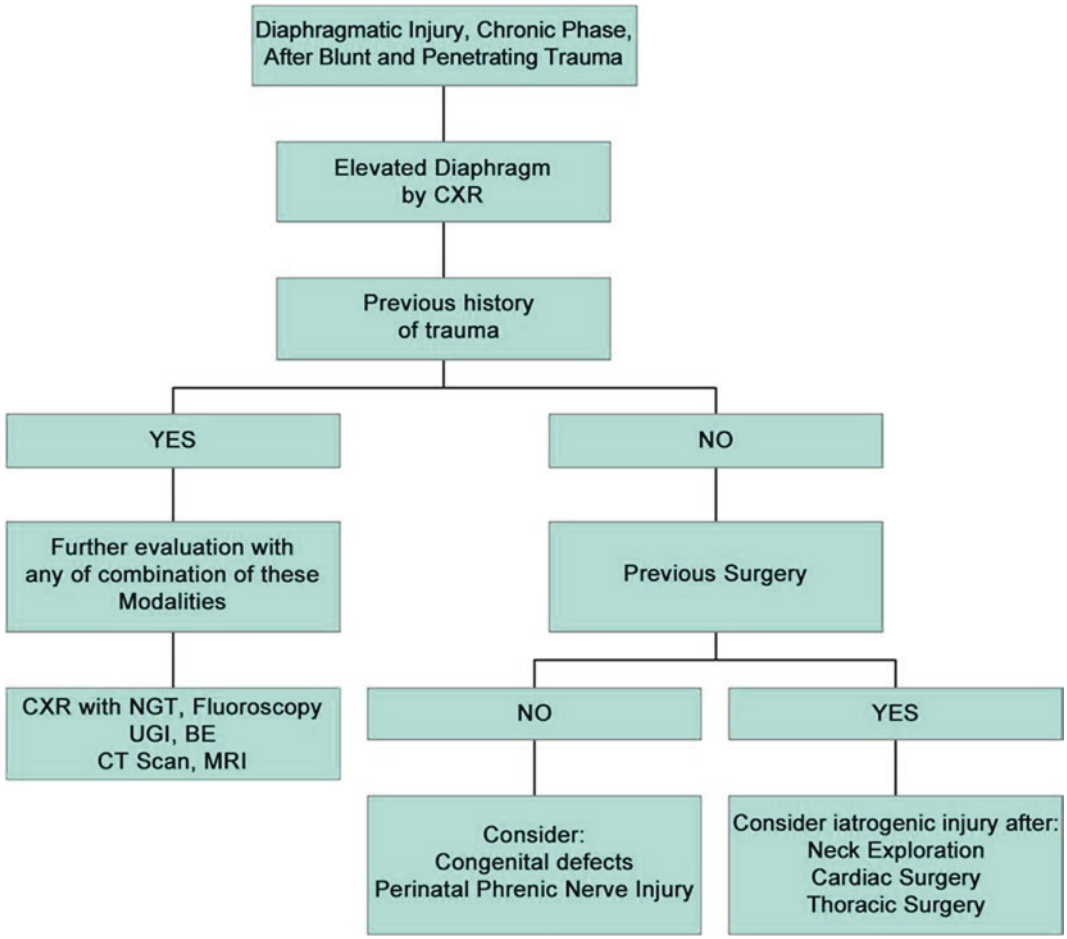

Fig. 2 Algorithm for diaphragmatic injury, chronic phase, after blunt and penetrating trauma. BE, barium enema; CT, computed tomography; CXR, chest radiograph; MRI, magnetic resonance imaging; NGT, nasogastric tube; UGT, upper gastrointestinal (adapted and reproduced with permission from Asensio, Petrone and Demetriades [13]). Diaphragmatic hernias can be either congenital or acquired. Congenital hernias may be located either anterior (Morgagni) or posterolateral (Bochdalek). Acquired hernias occur due to chronic enlargement of a natural hiatus, typically the esophageal hiatus, or traumatic injury of the diaphragm. These hernias may be repaired either via transthoracic or transabdominal approaches, each of which have specific advantages and disadvantages. In the current day, a minimally invasive, transabdominal approach is the most common method used to repair these hernias. Other pathologies, such as diaphragmatic elevation or eventration, can be treated with techniques such as diaphragmatic plication

strangulation of a diaphragmatic hernia as the arrest of the circulation of the affected organ due to compression. In his study, the description included: (1) a history of previous thoracic injury; (2) dullness or tympany in the lower portion of the left chest with aspiration of bloody fluid from the left pleural cavity; (3) radiographic findings suggestive of a high left diaphragm with displacement of the heart to the right; and (4) signs of acute gastrointestinal obstruction, particularly in the absence of abdominal distention. This author recommended

the use of a combined thoracoabdominal incision for the definitive surgical management of strangulated diaphragmatic hernias.

A series [22] of 53 cases of obstruction and strangulation in diaphragmatic hernias was reported due to sequelae of penetrating injuries. The interval between the initial diaphragmatic insult and the onset of symptoms averaged 4.6 years. The etiologic factor in the majority of the cases was a previous stab wound, and the most common herniated organs were the colon and the stomach, followed by the omentum in 40% of cases. Several authors have reported 20% mortality from incarceration and 40% to 57% mortality from strangulation of traumatic diaphragmatic hernias [10, 21–23].

Acute Intrapericardial Herniations

Rupture of the central tendon of the diaphragm involving the pericardium is rare. It can be caused by isolated trauma to the chest and abdomen, but the most common mechanism is a combination of forces to both cavities. Lacerations of the central tendon can be transverse, anteroposterior, and oblique. Jüttner [24] published the only case of herniation of intra-abdominal viscera into the pericardium, causing pericardial tamponade. However, the mortality in patients suffering this type of TDI is usually due to the severity of the associated injuries, such as blunt rupture of the heart, aorta, and/or tracheobronchial tree.

To illustrate, Van Loenhout [25] reported 58 cases of traumatic intrapericardial diaphragmatic hernia collected from the literature, with a high incidence of associated injuries. The organs most commonly noted to be herniating into the pericardium were the transverse colon, stomach, omentum, liver, and small bowel. Fulda et al. [26] reported a series of 22 patients admitted with blunt-traumatic pericardial rupture over a 10-year period in 20,000 patients admitted to their trauma center yielding an incidence of 0.1%. Five of the 22 patients (23%) died from the associated cardiac injuries.

Self-study

1. Missed diagnosis of TDI typically will have a clinical course over…
   a. Minutes to hours
   b. Days to weeks
   c. Months to years
2. Which statement is true?
   a. Thoracic approach is the preferred access for chronic post-traumatic diaphragmatic hernias.
   b. The correct approach will depend on the acuity of presentation, concern for difficulties reducing the hernia back into the abdomen, and surgical specialization of the surgeon.
   c. Abdominal approach is the preferred access for chronic post-traumatic diaphragmatic hernias.

Correct answers
Question 1: Answer c.
Question 2: Answer b.

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The Thoracoabdominal Border

Bronchobiliary Fistula

Yener Aydin, Ali Bilal Ulas, and Atilla Eroglu

Key Points

Bilioptysis is a rare reason of chronic cough that should arouse suspicion about the diagnosis of BBF.

Pulmonary complications may be mortal with overlapping bacterial superinfections.

Computed tomography for thorax and abdomen should be performed in patients with fever, chills or leukocytosis to assess any fluid collections.

Introduction

Bronchobiliary fistula (BBF) is a rare clinical condition that is characterized by abnormal and a defective passage between bronchial and biliary system. It is first reported in a liver hydatid cyst case in 1850 by Peacock [1]. BBF is usually caused by hepatic or subphrenic abscesses. It also leads to bilioptysis, which is a rare cause of a chronic cough. Diagnosis is usually based on clinical history and radiographic imaging. Endoscopic or surgical approaches are being used in treatment [2].

Etiology

The most common BBF reasons are liver hydatid cyst and amebic disease in developing countries, while trauma and biliary surgery complications in western countries are treated [3, 4]. However, Liao et al. [5] reported a review; a sum of 68 cases between 1980 and 2010, which mentioned tumors are the most common cause of BBF with a rate of 32.3%. In the literature, several BBF cases have been reported as a late period complication of cholelithiasis, choledocholithiasis, peptic ulcer disease, congenital imperfection, radiofrequency thermal ablation for hepatic tumors, hepatic resection, chronic pancreatitis, tuberculosis, biliary obstruction due to Ascaris lumbricoides, percutaneous transhepatic cholangiography and transcatheter arterial embolization [2–5].

Liver dome hydatid cyst rupture to thorax is a rare complication and is observed in 0.6–16% of hepatic hydatid cases [6]. Hepatic hydatid cyst opening to pleural space or bronch is a cause of high mortality and morbidity (9–43%) [7]. This is concluded with chemical pneumonitis due to biliary irritation [3].

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Pathophysiology

BBF is usually seen in the basilar segments of the right lung. Intense inflammation of bronchial mucosa due to bile leakage can cause acute pneumonia, bronchiolitis and chronic bronchopneumonia [4].

The classic clinical finding in these patients is an irritable cough. Two mechanisms are responsible for pathogenesis. In the first mechanism, the primary reason for fistula formation is biliary tract obstruction. Bile ducts obstruction may occur due to trauma, surgery, post-radiation scars, inflammatory diseases, foreign bodies, malignancy or granulomatous diseases. Eventually by bile retention, liver biloma and then abscess formation is seen. Growing abscesses erode diaphragm. In patients with a direct adhesion between lower lob and diaphragm due to passed pleural or lung pathologies, abscess reaches the nearest bronch and erodes lung parenchyma until BBF occurs. In patients without passed pleural pathologies, abscess erodes pleural space, creates pleurobiliary fistula (PBF) and leads empyema. In the second mechanism primary reason for fistula formation is the liver cyst and abscess. Abscesses are most often related to echinococcosis. Amoebic or pyogenic related abscesses also can be seen. Cysts and abscesses gradually grow and erode diaphragm. This may result in BBF or PBF formations [8]. Fistulas usually appear in the posteromedial side of the right hemidiaphragm.

Clinical Findings

Bilioptysis is the presence of bile in sputum and is a pathognomonic sign of BBF [8]. Bilioptysis characterized with yellowish sputum. In all of the cases, bilioptysis exists [5]. Bilioptysis should be considered in the presence of dark yellow, aqueous sputum. A persistent cough, fever, pain, and jaundice are other clinical features of BBF. Pneumonia is frequently seen due to bile irritation. Pulmonary complications may be mortal with overlapping bacterial superinfections.

Bile has a corrosive effect on the lungs and pleural space. PBF can lead to loculated biliary empyema and can cause trapped lung that suppresses lung functions by pleural adhesions. Bile presence revealed by analysis of bilirubin levels in pleural fluid and bilioptysis is pathognomonic for PBF [9]. In some cases, jaundice is mild or moderate. Generally, the clinical condition of the patients is not promising because of underlying chronic diseases or previous surgeries [2].

Diagnosis

Diagnosis of BBF is difficult and the most important thing that leads to a diagnosis is clinical suspicion. Because of very rare incidence of BBF, initially, diagnosis may be missed. When the presence of insist complaints, attention to surgical history about bile tract and not to neglect to see described yellowish sputum is essential for diagnose.

Injuries, jointly associated with liver, diaphragm, and lung may entail biliary-pleural or bronchobiliary fistula. Biliary drainage from inserted chest tube is diagnostic for biliary-pleural fistula.

Computed tomography for thorax and abdomen should be performed in patients with fever, chills or leukocytosis to assess any fluid collections. Thoracic and upper abdominal CT is the best method to plan further tests and assess lung and liver pathologies initially [4]. When effusion is detected, it must be drained and sent to culture test. Ultrasonography and computed tomography can assist in the detection of pathological conditions such as abscess, biloma, gallstones or tumors.

Imaging methods should be used for definitive diagnosis. Endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) is the most widely used methods for the diagnosis of BBF. Yet, a non-invasive method such as magnetic resonance cholangio and hepatobiliary iminodiacetic acid scintigraphy (HIDA) also provides a definitive diagnosis. However, ERCP or PTC, are used for the treatment of BBF as well as

diagnosis [2, 4, 10]. Bronchoscopic fistula identification is rarely in the literature [3, 11].

Treatment

There is not only a proposed method for treatment of BBF; each clinic's treatment method varies according to their experience. As well as minimally invasive methods such as nasobiliary drain or biliary stent via ERCP, there are also surgical options such as resection of fistula tract including liver and lung tissues [12–14]. There is no consensus on BBF treatment because of small number of cases reported in the literature. However, there is a tendency towards less invasive procedures. Endoscopic retrograde biliary drainage (ERBD), sphincterotomy, endoscopic nasobiliary drainage (ENBD) and endoscopic gallstone extraction are applied as therapeutic endoscopy to half of the patients. Percutaneous drainage and percutaneous transhepatic cholangial drainage (PTCD) are rarely used as the main treatment [5].

Nasobiliary drainage or endoscopic sphincterotomy via biliary endoprosthesis are some of the techniques used nowadays. These techniques have excellent results in the treatment of postoperative and posttraumatic biliary leaks. Nasobiliary drainage or endoscopic sphincterotomy with or without stenting has been reported as successful in the treatment of BBF [15–17]. Only endoscopic sphincterotomy or papillotomy with stenting combination may eliminate pressure gradient along Oddi sphincter and facilitate bile drainage. Depending this processing complications may occur like post-ERCP pancreatitis, bleeding or duodenal perforation [8, 11].

In patients with bile drainage preventing pathology, the first object is to provide passage transition. This significantly reduces bile leakage into the bronchial system. The treatment plan depends on the primary disease and the findings in the first assessment. Conservative approaches that provide adequate palliation such as biliary decompression by biliary stents or endoscopic sphincterotomy should be preferred in patients whose BBFs are developed due to malignant diseases and have a shortly expected survival. With higher rates of success, surgery is the recommended method in patients with absence of adequate drainage whose obstructions are connected to a benign disease like lithiasis or hydatid cyst [4, 8].

Surgical procedures are invasive and often used as the last option. Pulmonary lobectomy, resection of the fistula tract and supplementing with living tissue, hepalobectomy, hepaticoenterostomy, abscess drainage are surgical methods that are applied alone or as combined [5].

There is a thoracotomy indication in case of persistent biliary channel fistula. A delay in intervention causes more lung damage and pulmonary resection may be necessary. During thoracotomy, subdiaphragmatic area and the dome of the liver must be exposed and fistula tract must be completely explored. The tract is completely resected and the liver damage is repaired to prevent the bile leakage. Tocchi et al. [10] reported that they obtained successful results in 31 patients who underwent surgery. To support the repaired diaphragm with intercostal muscles and the pericardial fat pad is recommended to increase the success of surgery [18].

Liao et al. [5] have reported as therapeutic endoscopy safer than surgery (96.8% vs. 76.9%). It is submitted that treatment with conservative methods may be more successful approach and surgery should be preferable if these methods fail [9].

Over the past few years, new treatment methods such as bronchoscopy guided N-butyl cyanoacrylate embolization and radiofrequency ablation via endoscopic way have been reported. However, the effectiveness of these methods is controversial [12, 13].

Congenital Bronchobiliary Fistula

About 40 congenital BBF cases have been reported until now since first reported date 1952 [19]. Congenital BBF often manifests itself with recurrent pulmonary infections and accompanying atelectasis in early life. Girls are affected more often. Rarely, it can be diagnosed after

infantile period. Congenital BBF is most frequently characterized by the relation between right middle lobe bronchus and left hepatic duct. In some cases, diaphragmatic hernia and biliary atresia may be accompanied. Endoscopy or exploratory surgery is needed for definitive diagnosis. Bronchoscopy may show bronch that is opened to the fistula. Therefore it is recommended as a diagnostic method for congenital BBF. Recently, multidetector CT has been found useful in the diagnosis and treatment planning of congenital BBF. CT shows not only fistula but also inflammatory conditions. Cholecystography can be used to verify bile drainage into the duodenum. There is surgical indication when BBF is diagnosed. In the treatment, completely surgical excision of intrathoracic fistula tract portion is required. It may be necessary to resect the affected segments if fistula's hepatic part is not linked to biliary system or duodenum. BBF detected cases are usually treated with fistula division and ligation by approaching via right hemithorax. Hepatic lobectomy or Roux-en-Y hepaticojejunostomy may be required in patients with biliary drainage impairment or sepsis [20].

Conclusion

BBF is a rare but important clinical condition. In patients presenting with a persistent cough and bilioptysis, a careful clinical history should be taken, thoracic and abdominal pathologies should be evaluated radiologically. Purpose of BBF treatment is to ensure bile flow to duodenum in a comfortable way and reduce intrabiliyary pressure thus allow closure of the fistula tract. In treatment, endoscopic and conservative methods should be tried first and in case of failed surgical therapy should be preferred.

Self-study

1. Which statement is not true?
   (a) Intense inflammation of bronchial mucosa due to bile leakage can cause acute pneumonia, bronchiolitis and chronic bronchopneumonia.
   (b) Bilioptysis is the presence of bile in sputum and is a pathognomonic sign of BBF.
   (c) Biliary drainage from inserted chest tube is diagnostic for biliary-pleural fistula.
   (d) Resection of the fistula tract is the first step in the treatment of BBF.
2. Which statement is not true?
   (a) Hepatic hydatid cyst opening to pleural space or bronch is a cause of high mortality and morbidity (9–43%). This is concluded with chemical pneumonitis due to biliary irritation.
   (b) ERCP or PTC, are used just for the diagosis of BBF.
   (c) There is a thoracotomy indication in case of persistent biliary channel fistula.
   (d) Purpose of BBF treatment is to ensure bile flow to duodenum in a comfortable way and reduce intrabiliyary pressure thus allow closure of the fistula tract.

Answers

1. Which statement is not true?
   (a) Intense inflammation of bronchial mucosa due to bile leakage can cause acute pneumonia, bronchiolitis and chronic bronchopneumonia.
   (b) Bilioptysis is the presence of bile in sputum and is a pathognomonic sign of BBF.
   (c) Biliary drainage from inserted chest tube is diagnostic for biliary-pleural fistula.
   (d) Resection of the fistula tract is the first step in the treatment of BBF (**Surgical procedures are invasive and often used as the last option.)—CORRECT**.
2. Which statement is not true?
   (a) Hepatic hydatid cyst opening to pleural space or bronch is a cause of high mortality and morbidity (9-43%). This is concluded with chemical pneumonitis due to biliary irritation.
   (b) ERCP or PTC, are used just for the diagosis of BBF **(ERCP or PTC, are used for the treatment of BBF as well as diagnosis.)—CORRECT**.
   (c) There is a thoracotomy indication in case of persistent biliary channel fistula.

(d) Purpose of BBF treatment is to ensure bile flow to duodenum in a comfortable way and reduce intrabiliyary pressure thus allow closure of the fistula tract.

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Subphrenic Abscess

Yener Aydin, Ali Bilal Ulas, and Atilla Eroglu

Key Points

- The mortality rate is increased in cases where the abscesses cover multiple spaces or in abscesses that are developed after urgent interventional procedures.
- The best results are obtained by continuing antibiotic treatment after draining abscesses by surgically or with drainage.
- Firstly, percutaneous drainage by catheter guidance should be applied and if needed surgical drainage should be considered.

Introduction

Subphrenic abscess is a collection of purulent or infected fluid in the gap between diaphragm and liver or spleen. Subphrenic abscess may be developed after any abdominal surgery. It is seen in approximately 3–6 weeks after abdominal surgery. In elderly patients, it tends to be seen more. The pus accumulates under diaphragm usually comes from other locations in abdomen. In about half of the cases, subphrenic abscess is seen on the right side, while 1/4 in the left side and 1/4 simultaneous bilateral [1, 2].

Subphrenic Space

Right subphrenic space shows continuity with right subhepatic space and right pericolic space. Right subphrenic space extends with adjacent to lateral and superior parts of liver. In axial and coronal images, the posterior margin of the subphrenic area ends at the anterior margin of the coronary ligaments. Right subphrenic space is limited in midline by the falciform ligament in upper part of abdomen. Due to variability in length of ligament, it may achieve or not, to be an effective barrier against fluid spread to the left side [3, 4].

The left subphrenic space is under left the diaphragm and surrounds the gap between front portion of gastric fundus, liver, spleen, and stomach. Fluids may accumulate in anterior or posterior section of this space. The left subhepatic section immediately continues with front part of left subphrenic area. Lateral perisplenic section immediately continues with left pericolic space. The phrenicocolic ligament rarely acts as an effective barrier, though it is theoretically known that it limits the migration of fluids from left pericolic space to left subphrenic space. In most cases, it has been shown that this ligament

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has an inadequate barrier function against infection regardless of alterations in its length, shape, and localization [1, 5].

Etiology

In the etiology, intraperitoneal perforations are responsible such as duodenal ulcer, diverticulitis, appendicitis, amoebic liver abscess. Pathogens are mostly polymicrobial and generally include Escherichia coli, Enterococcus spp, Bacteroides fragilis and Clostridium spp. Secondary reasons in the etiology are surgical interventions, critical diseases and abdominal traumas. In this instance, frequently pathogens are Candida spp, Enterococcus spp, Enterobacter spp, Staphylococcus epidermidis and E. coli. It is usually polymicrobial and almost anaerobic bacterias and aerobic bacterias play an equal role except post-biliary surgeries. Mukhopadhyay et al. [6] has detected subphrenic abscesses developed in 3 of the 72 cases of amoebic liver abscess. Bufalara et al. [7] has reported intra-abdominal abscess rate as 1.6% in postoperative periods.

Various diseases can cause a right subphrenic abscess. Because this area has a free passage through from right pericolic gutter and right subhepatic recess. However, the most common cause of abscess in this region is appendicitis or intra-abdominal organ perforations. Abscess may be entirely in liquid density or may contain gas.

Left subphrenic abscesses can be caused by a number of abnormalities. Abscess' typical sources are gastric ulcers, postoperative leakages, tumor perforations, esophagus or left colon. In some of esophageal perforation cases, inflammatory process is seen in retroperitoneal zone rather than subdiaphragmatic zone. However, if a portion of stomach is affected, subdiaphragmatic zone may be affected too [1, 2, 4].

Clinical Findings

In cases with subphrenic abscess, fever and chills occur. In the history of the cases, there are undergone abdominal operations about one month ago and newly appeared loss of appetites. There is an abdominal pain on the side of abscess. It is usually accompanied by a cough and respiratory distress. When the fluid in the subphrenic area passes into the pleural space, respiratory sounds decrease or disappear completely. In some cases, hiccups may be seen due to diaphragmatic irritation. Shoulder pain may occur on the abscess side.

The examination usually involves fever, tachycardia, non-productive cough, reduced breathing sounds, skin edema, tenderness between eighth and twelfth ribs, chronic hiccups, tenderness and swelling in abdomen, decreased bowel sounds, jaundice, and acid in abdomen. Patients are often bewildered and have confused appearance [1, 2, 4].

Diagnosis

If the diagnosis of subphrenic abscess is delayed or cannot be made, patients may die because of septic shock. Therefore, careful examination and radiological evaluation are required. Subphrenic abscess has a favorable outcome via accurate diagnosis, appropriate and rapid treatment.

Especially in postoperative period after a laparotomy or after intra-abdominal organ ruptures, presence of the above findings is cautionary for the diagnosis. However, in patients with no history of operations, subphrenic abscess diagnosis may be overlooked.

Complete blood count (CBC), sedimentation, blood and urine culture are performed during suspected subphrenic abscesses. Abdominal radiography, barium graphy, IVP, passage graphy can be useful in the diagnosis. Abscesses are usually visualized by abdominal ultrasonography and computerized tomography. MRI is also useful in the diagnosis [8–10].

Separation of Subphrenic Abscess from Pleural Effusion

The most important diagnostic point of the right subphrenic abscess is the ending of peritoneal cavity in coronary ligaments next to liver.

Subphrenic abscess should not be confused with pleural effusion. If the fluid remains behind the posterior fatty tissue of liver, it indicates pleural effusion. In this case, subphrenic abscess is excluded. Any fluid or gas remaining in the fat tissue in this area is at the top of the retroperitoneal space. If the patient has both pleural effusion and a subphrenic abscess, decubitus position may allow the pleural fluid to move, thus confirming the diagnosis. Rarely, in some cases visualization of diaphragm, that is rich in blood supply, may be needed by dynamic imaging with contrast agent injection. Any fluid in the subphrenic cavity may be seen as abscess, even if it is bile, blood, necrotic tumor or loculated ascites.

Pleural effusions on the left side should be differentiated with left subdiaphragmatic abscesses. The area between upper pole of spleen and left kidney, which is containing splenic pedicle and tail of pancreas represents the splenorenal ligament. This region behind the fatty tissue is within the pleural space, not the subdiaphragmatic peritoneal space. Any fluid in this region is at the top of the retroperitoneum rather than the left subdiaphragmatic space. Fluids above the splenorenal ligament may completely accumulate around the spleen and interpose between the diaphragm and the spleen. In case of any problem in distinguishing pleural effusions from subphrenic collections, patients should be lien in decubitus position. If the pleural fluid is large and under pressure, it can easily be misdiagnosed as abscess. A large pleural effusion is seen adjacent to diaphragm. At first glance, it is difficult to distinguish pleural effusion from subphrenic collection. However, careful examination shows the fluid is behind spleen. To detect a small abscess in the left subdiaphragmatic area, oral contrast material should be injected and stomach should be filled. A stomach filled with fluid may sometimes be likened to an abscess or vice versa. Contrast agents make it clear and remove any doubt about the diagnosis [11, 12].

Treatment

Subphrenic abscesses are treated by draining the abscess and using appropriate antibiotics such as treatment of any abscesses in any part of the body. There should be no delay in treatment of subphrenic abscess considered patients to prevent expansion of thoracoabdominal spread. Firstly, percutaneous drainage by catheter guidance should be applied and if needed surgical drainage should be considered.

It must be evaluated whether subphrenic abscesses have an extension to the adjacent anatomical regions or not. In cases of right subphrenic abscesses, drainages of right subhepatic and right pericolonic fields may require. Left subphrenic abscesses may extend into the right subphrenic, left subhepatic and left pericolonic fields [13]. When drainage is performed, catheter should be placed with visualizing pleural space, gallbladder and hepatic flexure of the colon and attention should be paid not to injure these structures. Patients should be lien to lateral or decubitus positions if there is a problem in localizing subphrenic abscesses or in distinguishing liver from hepatic flexure of colon.

In the treatment of intra-abdominal abscesses, percutaneous drainage is the primary treatment option for appropriate localized abscesses. Drainage catheter is placed by CT or ultrasound guidance. Avoidance from pleural space is important to prevent pneumothorax and thorax infection. Typically, pleural space extends to 8. thoracic vertebrae in anterior, 10. thoracic vertebrae in lateral and 12. thoracic vertebrae in posterior. These lines can be used to prevent penetration of pleural cavity. Some subphrenic fluid collections may not allow extrapleural approach. In this case, surgical drainage should be considered due to increased risk of pneumothorax and empyema because of transpleural percutaneous abscess drainage [7, 8, 14, 15].

Surgery is the main treatment of subphrenic abscesses today. However operative mortality is high [7, 8]. Percutaneous drainage is another treatment option. Although this is associated with significant morbidity [7, 14]. Bufalara et al. [7] found no significant difference in morbidity, mortality and duration of drain tube between surgical drainage and percutaneous drainage in postoperative intra-abdominal abscesses. However, percutaneous drainage has been proposed for less invasiveness and lower cost [7]. Due to close location of subphrenic location to lung and pleural space, it is considered as a particularly problematic area for percutaneous abscess drainage with imaging guidance. Despite these risky areas, percutaneous drainage continues to be a preferred method of treatment for subphrenic abscesses [16]. Many researchers suggest an angled subcostal approach to protect against pleural complications of percutaneous abscess drainage in this area [1, 14]. Preece et al. [16] evaluated the results of intercostal approaches (214 patients) and subcostal approaches (186 patients) that were applied to 258 patients with single or multiple subphrenic abscesses. The number of pleural complications were significantly higher in the intercostal group than in the subcostal group (26.2% vs. 8.1%, $p<0.001$). Pneumothorax was seen in 15 cases in the intercostal group and no pneumothorax was seen in the subcostal drainage group. Similarly, the incidence of new or increased pleural effusion was significantly higher in the intercostal group (17.8% vs. 7.5%, $p<0.01$). Empyema incidence was low and similar between the two groups (1.4% in the intercostal group and 0.5% in the subcostal group).

Subphrenic abscess causes serious complications if is not treated effectively. An abdominal cavity that cannot be reached with a laparoscopic approach due to adhesions can cause a high risk of percutaneous drainage failure and redo-laparotomy cases may prevent effective treatment. In this case, a new approach is needed for the right subphrenic collections. Alassar et al. [17] reported that laparoscopic drainage could be achieved by entering the pleural cavity through the tenth intercostal space and creating a small diaphragmatic window. Goulet [18] has reported a successfully treat of a right subphrenic abscess via endoscopic transgastric drainage that is not appropriate for percutaneous drainage. Seewald et al. [9] has reported successful treatment of left-sided subphrenic abscesses with EUS-guided drainage in two cases. EUS-guided drainage was presented as an effective and safe option in the treatment of subphrenic abscesses. EUS-guided drainage has several advantages. Localization and anatomy of the subphrenic space are revealed in a perfect way. Transducers can be placed closely to the abscess cavity. When the needle passes directly from stomach wall to abscess space, accidental injuries of lung and pleura are prevented. The use of Color Doppler US prevents injuries to the intervening veins. Transcutaneous infections are also prevented [9]. The usual complication of abscess drainage with EUS is obstruction of the stent, which is why many authors suggest that a few stents should be placed [19].

In general, the rate of cure for the subphrenic collections is between 79 and 85%. Complications are empyema and sepsis and the incidence is up to 2% [14, 20].

Prognosis

Subphrenic abscesses continue to be associated with high mortality, despite wide spectrum antibiotics and surgical techniques. Overall mortality rate is 31%. The mortality rate is increased in cases where the abscesses cover multiple spaces or in abscesses that are developed after urgent interventional procedures [1]. Mortality reasons are usually uncontrolled infections, malnutrition, and post-operative secondary infections. The best results are obtained by continuing antibiotic treatment after draining abscesses by surgically or with drainage.

Conclusion

The majority of subphrenic abscesses are postoperative. Previous laparoscopic or open abdominal surgeries, blunt or penetrating traumas, gastrointestinal perforations (may be due to malignancy, appendicitis or diverticulitis), inflammatory bowel diseases, and immunocompromised patients constitute a risk to subphrenic abscesses. There is also a risk of perioperative sepsis in patients with subphrenic abscess. Care should be taken to surgical complications and clinicians should be alerted to clinical symptoms in order to minimize morbidity and prevent mortality.

Self-study

1. Which statement/statements is/are true?
   (a) Subphrenic abscess may be developed after any abdominal surgery.
   (b) It is seen in approximately 3–6 weeks after abdominal surgery.
   (c) In some cases, hiccups may be seen due to diaphragmatic irritation.
   (d) Shoulder pain may occur on the abscess side.
   (e) a, b, c, d.
2. Which statement/statements is/are true?
   (a) Previous surgeries, traumas, gastrointestinal perforations, inflammatory bowel diseases, and immunocompromised patients constitute a risk to subphrenic abscesses.
   (b) In the treatment of intra-abdominal abscesses, percutaneous drainage is the primary treatment option for appropriate localized abscesses.
   (c) Surgery is the main treatment of subphrenic abscesses today.
   (d) Mortality reasons are usually uncontrolled infections, malnutrition, and postoperative secondary infections.
   (e) a, b, c, d.

Answers

1. Which statement/statements is/are true?
   (a) Subphrenic abscess may be developed after any abdominal surgery.
   (b) It is seen in approximately 3–6 weeks after abdominal surgery.
   (c) In some cases, hiccups may be seen due to diaphragmatic irritation.
   (d) Shoulder pain may occur on the abscess side.
   (e) a, b, c, d **(CORRECT)**.
2. Which statement/statements is/are true?
   (a) Previous surgeries, traumas, gastrointestinal perforations, inflammatory bowel diseases, and immunocompromised patients constitute a risk to subphrenic abscesses.
   (b) In the treatment of intra-abdominal abscesses, percutaneous drainage is the primary treatment option for appropriate localized abscesses.
   (c) Surgery is the main treatment of subphrenic abscesses today.
   (d) Mortality reasons are usually uncontrolled infections, malnutrition, and postoperative secondary infections.
   (e) a, b, c, d **(CORRECT)**.

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Carcinoma of the Upper Pole of the Stomach and Gastroesophageal Junction

Kazuo Koyanagi and Soji Ozawa

Key Points

- Although the Siewert classification has been widely accepted for the definition of carcinoma of the EGJ, recently published 8th edition of UICC-TNM classification introduces new concept of carcinoma of the EGJ.
- Surgical strategy for carcinoma of the EGJ should be determined by tumor invasion of the esophageal and gastric wall and the relative risk of mediastinal lymph node metastasis.
- Esophageal invasion length (EIL) and gastric invasion length (GIL) should be determined and can be used for deciding the range of esophageal or gastric resection and area of dissecting lymph node.
- Abdominal transhiatal and transthoracic approaches are selected according to preoperative diagnosis and oncological safety.
- Minimally invasive approach using laparoscopic and thoracoscopic surgery will results in a lower incidence of morbidity and mortality after surgery for carcinoma of the EGJ.

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Introduction

The worldwide incidence of carcinomas of the esophagogastric junction (EGJ) has been increasing in the past few decades [1]. Carcinomas of the EGJ are located at the thoracoabdominal border between esophagus and the stomach. This entity of the disease includes not only the true EGJ carcinoma, but also distal esophageal and upper pole of the gastric carcinoma. There are two major histopathological types of carcinomas located at the EGJ; adenocarcinoma and squamous cell carcinoma. In the Western countries, adenocarcinoma is dominant and is widely believed to be associated with increased body weight, gastroesophageal reflux disease, and premalignant Barrett epithelium. In contrast, especially in the East Asian countries, squamous cell carcinoma accounts for the majority of the esophageal carcinomas and esophageal adenocarcinoma remains very low.

The diagnosis as well as deciding the therapeutic strategy for the carcinoma of the EGJ is challenging. The selection of the appropriate surgical procedure has been decided based on the pre-operative diagnostic staging, using esophagogastrography, esophagogastroscopy, CT scan, and PET/CT. However, clinical determination of esophagogastric junction is difficult in some cases and potential oncological malignancy may be different according to the location of the tumors. Differences in pathological types

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may affect the decision of the surgical strategy. Furthermore, from a clinical point of view, the surgical strategy for EGJ carcinomas is mainly determined by tumor invasion of the esophageal and gastric wall and the relative risk of the mediastinal lymph node metastasis [2–4]. In this chapter, we describe the surgical approaches for carcinomas of the EGJ based on the recent advances of diagnosis and treatment.

Classification and Staging of Carcinoma of the EGJ

The Siewert classification has been widely accepted to define the adenocarcinoma of the EGJ (Fig. 1) [5]. This classification divides this entity into three subtypes according to its anatomical localization relative to the EGJ. Siewert type I is esophageal adenocarcinoma arising from 1 to 5 cm above the EGJ. Barrett's esophagus is the main risk factor for the development of esophageal adenocarcinoma along with the presence and degree of dysplasia. Siewert type II is considered as true EGJ adenocarcinoma. Epicenter of the tumor is located within 1 cm proximal and 2 cm distal to the EGJ. Siewert type III is a subcardial gastric adenocarcinoma invading the EGJ, and the epicenter is located within 2–5 cm distal from the EGJ. Many studies have been conducted using the Siewert classification, however, it can be used only for adenocarcinoma, not for squamous cell carcinoma. The EGJ is usually defined as distal end of the lower esophageal palisade vessels or as upper ends of the gastric mucosal folds by endoscopic examination and is defined as the narrowest locus of the lower esophagus by esophagogastrography. However, overall accuracy in predicting tumor location according to the Siewert classification was around 70% [6].

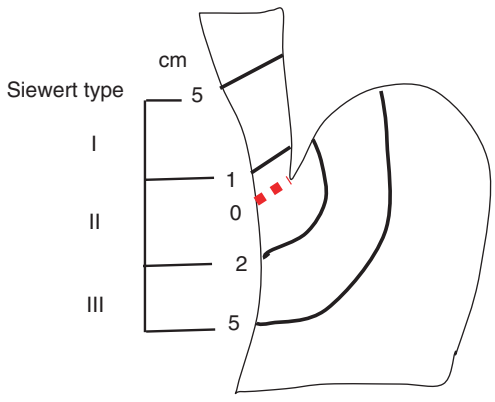

Fig. 1 Siewert classification

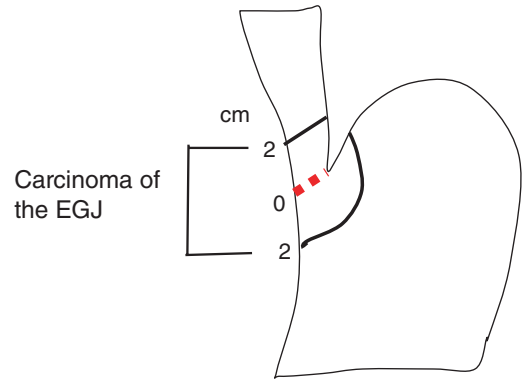

Fig. 2 UICC-TNM classification ver. 8

On the other hand, UICC-TNM classification includes any types of pathology except for melanoma. The 7th edition of the International Union Against Cancer TNM Classification of Malignant Tumors [7] divided the carcinoma of the EGJ into two subtypes according to the epicenter of the tumor and its extension: esophageal EGJ tumor and gastric EGJ tumor. Esophageal EGJ tumor was defined as the tumor in which epicenter of the tumor was located within 5 cm proximal to the EGJ or the tumor arising within 5 cm distal from the EGJ with invasion into the esophagus. Gastric EGJ tumor was defined as the tumor arising within 5 cm distal from the EGJ without invasion into the esophagus. However, this classification has not been widely accepted in clinic because it could not be used appropriately for the tumor located at the thoracoabdominal border. The latest 8th edition of TNM Classification (UICC 2017) has changed the concept of EGJ tumors (Fig. 2) [8]. In the new classification rules, a tumor with an epicenter within 2 cm of the EGJ and also extends into the esophagus is classified and staged using esophageal scheme, and

cancers involving the EGJ with an epicenter of within the proximal 2 cm of the cardia (Siewert types I/II) are to be staged as esophageal cancer. Cancers whose epicenter is more than 2 cm distal from the EGJ will be staged using the stomach cancer TNM and Stage even if the EGJ is involved. This new classification is similar to the Japanese Classification of the Esophageal Cancer [9], that is, majority of Siewert type I and type II tumors are considered to be carcinoma of the EGJ and the Siewert type III tumor is defined as gastric carcinoma.

Consensus of Surgical Procedures

Surgical procedures for carcinoma of the EGJ has been performed mainly according to the Siewert classification. Siewert type I and type III tumors are usually treated as esophageal and gastric tumors, respectively. Because of the higher risk of mediastinal lymph node metastasis, a transthoracic and abdominal approach is frequently used for Siewert type I tumors; whereas an abdominal or transhiatal approach is commonly proposed for Siewert type III tumors. On the other hand, the optimal surgical approach for the Siewert type II tumor remains unclear. Although the dissection of the lower mediastinal lymph nodes can be performed via either a transthoracic or transhiatal approach, only a transthoracic method can be used to dissect the upper and middle mediastinal lymph nodes. Furthermore, following the proposal of a new UICC-TNM classification, it is necessary to optimize the surgical strategy that can be used for squamous cell carcinoma of the EGJ.

Since an R0 resection is essential for long term survival after surgery for carcinoma of the EGJ, the extent of lymph node dissection should be considered as well as the extent of esophageal or gastric resection in individual carcinoma of the EGJ. Lymph node metastasis is known as a prognostic factor. However, the accuracy of preoperative assessments of positive lymph node metastasis in patients with carcinoma of the EGJ is not yet as high as needed [6]. The longitudinal lymphatic flow is very rich in submucosal layer of the esophageal wall; however, the incidence of mediastinal lymph node metastasis is very low when the tumor is predominantly located in the abdominal cavity and has not invaded the thoracic cavity [10]. Therefore, surgical strategy for carcinoma of the EGJ should be determined by tumor invasion of the esophageal and gastric wall and the relative risk of upper and middle mediastinal lymph node metastasis. This strategy can be used for both adenocarcinoma and squamous cell carcinoma.

Distance from the EGJ to the Edge of the Carcinoma

Esophageal invasion length (EIL), defined as the distance from the EGJ to the proximal edge of tumors of the EGJ has become a focus to decide the appropriate surgical strategy of this entity [1, 4, 11]. An EIL of more than 25 mm may be a significant predictor of upper and middle mediastinal lymph node metastasis. An EIL of more than 25 mm also means that carcinoma of the EGJ invades into thoracic cavity. Considering the latest 8th UICC-TNM classification, when carcinoma of the EGJ locates or invades in thoracic cavity, transthoracic approach should be recommended because mediastinal lymph node dissection can be performed safely and promptly. On the other hand, upper and middle mediastinal lymph node metastasis or recurrence may be rare in carcinoma of the EGJ with less than 25 mm of an EIL. Therefore, when carcinoma of the EGJ still locates in abdominal cavity, transhiatal approach with lower mediastinal lymph node dissection should be recommended.

As same as an EIL, gastric invasion length (GIL), defined as the distance from the EGJ to the distal edge of tumors of the EGJ has been shown as the surrogate of nodal involvement along the greater curvature or antrum [12]. A GIL can be used for deciding the range of stomach resection. A GIL of more than 50 mm may be a significant predictor of lymph node metastasis along the greater curvature or antrum. Considering the latest 8th UICC-TNM classification, a GIL of more than 50 mm means that

this entity should be treated with stomach carcinoma and total gastrectomy with lymph node dissection should be recommended. On the other hand, lymph node metastasis along the greater curvature or antrum may be rare in carcinoma of the EGJ with less than 50 mm of a GIL. In such cases, proximal gastrectomy, not total gastrectomy, should be preferred.

Abdominal and Transhiatal Approach

Approaches and surgical techniques for carcinoma of thoracoabdominal border is summarized in Table 1. Standard surgical approach for Siewert type III tumor is abdominal approach that contemplates an extended total gastrectomy with D2 lymph node dissection [13]. Modified D2 lymph node dissection (so-called D1+; excluding splenectomy and dissection the lymph node of splenic hilum) has been proposed to reduce the postoperative complications. When the tumor invaded to esophageal wall (thoracoabdominal border), transhiatal resection of distal esophagus and lower mediastinal lymph node dissection should be performed [14]. Reconstruction is performed by esophagojejunostomy and Roux-en-Y anastomosis.

In the cases of early carcinoma of the EGJ, more limited operation such as proximal gastrectomy without lymph node dissection along the greater curvature or antrum should be performed. Stomach tube or jejunal interposition can be used for reconstruction.

Table 1 Approaches and surgical techniques for carcinoma of thoracoabdominal border

1. Location of the tumor
• Esophagus
• Stomach
• Esophageal invasion length
• Gastric invasion length
2. Risk of lymph node metastasis
• Mediastinal
• Perigastric
• Esophageal invasion length
• Gastric invasion length
3. Surgical oncology
• Proximal margin
• Distal margin
• Mediastinal lymph node dissection
• Along greater curvature and antrum lymph node dissection
4. Incision
• Abdominal
• Transhiatal
• Transthoracic and abdominal
5. Resection
• Total gastrectomy
• Total gastrectomy + Lower esophagus
• Proximal gastrectomy + Lower esophagus
• Thoracic esophagus + Proximal gastrectomy
6. Lymph node dissection
• Abdominal
• Abdominal + Lower mediastinal
• Upper abdominal + Lower mediastinal
• Extended mediastinal + Upper abdominal
7. Reconstruction
• Roex-en-Y
• Jejunal interposition
• Stomach tube
• Colon interposition

Transthoracic and Abdominal Approach

Approaches and surgical techniques for carcinoma of thoracoabdominal border is summarized in Table 1. To secure the proximal margin safely, carcinoma of the EGJ invading to the thoracic cavity should be treated via transthoracic approach. Also, for carcinoma of the EGJ with higher risk of middle or upper mediastinal lymph node metastasis, middle and upper mediastinal lymph node dissection should be performed via transthoracic approach. Therefore, transthoracic approach is preferably indicated to carcinoma of the EGJ located or invaded in thoracic esophagus.

Transthoracic approach is more invasive and postoperative complications such as pneumonia and recurrent laryngeal nerve paralysis should be considered [15, 16]. The decision for one procedure over the other was taken preoperatively according to the results of preoperative diagnosis or intraoperatively in some cases by the surgeons. Although there has been no systematic tool for decision making, an EIL or a GIL may be a new predictive factor to decide the surgical strategy for carcinoma of the EGJ.

Minimally Invasive Approach

Laparoscopic and thoracoscopic surgery have been attracting attention as a minimally invasive approach for the treatment for both benign and malignant diseases [17]. Laparoscopic and thoracoscopic surgery can be associated with a lower operative blood loss, a shorter intensive care unit and hospital stay, and a reduction in postoperative respiratory complications. Standardization of the minimally invasive technique for gastric and esophageal carcinoma is being established. Recently, this minimally invasive technique has allowed for carcinoma of the EGJ, however, standardization for this entity is still challenging. Minimally invasive approach for carcinoma of the EGJ may reduce the postoperative morbidity and mortality rates.

Robotic surgery is being introduced for esophageal and gastric cancer. Robotic surgical systems may allow surgeons to overcome many of obstacles associated with laparoscopic or thoracoscopic surgery, enabling more technical adaptation [18]. Surgical approach for carcinoma of the EGJ is complicating, therefore, robotic surgery may contribute to reduce the postoperative morbidity after minimally invasive surgery.

Summary

Carcinomas of the EGJ are located at the thoracoabdominal border between esophagus and the stomach. This entity of the disease includes not only the true EGJ carcinoma, but also distal esophageal and upper pole of the gastric carcinoma. The Siewert classification has been widely accepted to define the adenocarcinoma of the EGJ. On the other hand, concept of the latest 8th edition of TNM Classification is different from the Siewert classification. This new classification rules clearly indicates that carcinoma of the EGJ locates within 2 cm of the EGJ. However, surgical strategy for carcinoma of the EGJ should be determined by tumor invasion of the esophageal and gastric wall and the relative risk of upper and middle mediastinal lymph node metastasis. This strategy can be used for both adenocarcinoma and squamous cell carcinoma. An EIL and a GIL may be used for deciding the range of esophageal or gastric resection and area of dissecting lymph node. Abdominal, transhiatal, and transthoracic approaches are selected according to preoperative diagnosis and oncological safety.

Self-study

(1) Which is wrong as a classification of carcinoma of the EGJ?
   (A) Siewert type I is esophageal adenocarcinoma arising from 1 to 5 cm above the EGJ.
   (B) Siewert type II is considered as true EGJ adenocarcinoma.
   (C) In the 7th edition of the UICC-TNM Classification, esophageal EGJ tumor is defined as the tumor in which epicenter of the tumor is located within 5 cm proximal to the EGJ or the tumor arising within 5 cm distal from the EGJ with invasion into the esophagus.
   (D) In the 8th edition of the UICC-TNM Classification, a tumor with an epicenter within 2 cm of the EGJ and also extends into the esophagus is classified and staged using esophageal scheme, and cancers involving the EGJ with an epicenter of within the proximal 2 cm of the cardia (Siewert types I/II) are to be staged as esophageal cancer.
   (E) The UICC-TNM classification cannot be used for squamous cell carcinoma.

(2) Which procedure is suitable as surgical procedure for carcinoma of the EGJ?
   (A) Transthoracic and abdominal approach for early Siewert type III adenocarcinoma.
   (B) Upper mediastinal lymph node dissection for early carcinoma at the EGJ.
   (C) Total gastrectomy for localized thoracic esophageal adenocarcinoma.
   (D) Transthoracic and abdominal approach for carcinoma of the EGJ invading to lower thoracic esophagus.
   (E) Abdominal and transhiatal approach for large carcinoma of the EGJ invading to lower thoracic esophagus more than 4 cm from the EGJ.

Answer

(1) Which is wrong as a classification of carcinoma of the EGJ?
   (A) Yes.
   (B) Yes.
   (C) Yes.
   (D) Yes.
   (E) No. (**Correct answer**)

(2) Which procedure is suitable as surgical procedure for carcinoma of the EGJ?
   (A) Transthoracic and abdominal approach is not necessary for early Siewert type III adenocarcinoma.
   (B) Upper mediastinal lymph node dissection is not necessary for early carcinoma at the EGJ.
   (C) Transthoracic approach is necessary for thoracic esophageal adenocarcinoma.
   (D) Yes. (**Correct answer**)
   (E) Transthoracic and abdominal approach is necessary.

Conflict of Interest The authors have no potential conflicts of interest to disclosure.

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Approaches and Surgical Techniques for Esophageal Achalasia, Hiatal Hernia and GERD (Gastro-Esophageal Reflux Disease)

Andreas Hecker, Birgit Hecker, Matthias Hecker, Ingolf Askevold, Winfried Padberg, and Martin Reichert

Key Points

- To perform functional surgery of the upper GI tract requires the particular knowledge of the anatomy and physiology of the lower esophagus sphincter (LES) and the esophagogastric junction (EGJ).
- Both Heller myotomy and modern endoscopic approaches (e.g. POEM) are effective treatment options for achalasia. Indications depend on the type of achalasia according to the Chicago Classification
- The subtype of hiatal hernia is of clinical relevance for the thoracic surgeon. While axial hernia are regular findings in patients with GERD the paraesophageal hernia bears the risk of incarceration with concomitant ischemia.
- PPIs and fundoplication techniques are effective treatment strategies for GERD. Laparoscopic (semi-)fundoplication is gold standard. Thoracic approaches are indicated in cases of redo surgery, shortening of the esophagus and synchronous thoracic surgery. Furthermore in cases of massive obesity a thoracic approach could be favored.

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Introduction

Functional disorders of the upper gastrointestinal tract are a challenge for thoracic and general surgeons. They do not only require a detailed knowledge of the anatomic situation at the esophagogastric junction (EGJ), but furthermore necessitate an individualized interdisciplinary diagnostic and therapeutic approach. Modern therapy is based on the three columns conservative/pharmaceutic, endoscopic/interventional and surgical treatment and should be evaluated in interdisciplinary boards to generate a tailored approach for the patient. While the laparoscopic access is the gold standard for the surgical

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therapy of both esophageal achalasia, hiatal hernia or/and gastroesophageal reflux disease the thoracic surgeon has to gain knowledge on the sophisticated thoracic operation techniques and accesses to the EGJ from the thoracic site. Key concept of the book chapter is to impart knowledge on the indications for a thoracic correction of these functional disorders. This requires, of course, a motivated study of standard operations and indications from the field of visceral surgery.

The esophagus enters the abdominal cavity through the muscular portion of the diaphragm. The diaphragmatic crura form the anterior and lateral margins of the esophageal hiatus. The median arcuate ligament is its posterior border. For the surgeon it is of elemental importance to know, that the anterior and posterior vagal trunks and the esophageal branches of the left gastric vessels as well enter the abdominal cavity through the esophageal hiatus. Any impairment of vascular supply or of vagal innervation could lead to serious functional complications after surgical intervention.

Functional surgery of the upper GI tract is complex and requires a fundamental knowledge on the anatomy and physiology of the esophagogastric junction. The anatomic situation is complicated by the fact that the lower esophageal sphincter (LES) is less an anatomic structure, but a more physiologic sphincter consisting of the so-called 'high-pressure zone' at the esophagogastric junction. Note that its function as a LES depends on the length of the tubular esophagus inside the abdominal cavity, the so-called 'angle of His' (=angle between the lower esophagus and the stomach), the phrenoesophageal ligament and the diaphragmatic crura. Furthermore the endocrine effects like NO-production etc. are important factors for the pathophysiology of functional upper GI diseases. While the esophagogastric junction can be easily identified by the endoscopist as the oral margin of the gastric folds (which corresponds with a pinching at the end of the tubular esophagus and the diaphragmatic indentation in most patients), the LES is just a relative stenosis proximal to the EGJ. For any kind of functional surgery the understanding of this complex area of the human body is essential. Restoring a physiological anti-reflux function of the LES requires this detailed knowledge, because essential surgical steps are deduced. As an example key feature of surgical anti-reflux therapy is the repositioning of up to 4 cm of the distal, tubular esophagus down under the diaphragm.

In the following the three fields of upper GI functional surgery Achalasia, Hiatal Hernia and Gastroesophageal Reflux Disease (GERD) will be explained in detail.

Achalasia

'Achalasia' is clinically and functionally defined by a constantly increased pressure of the functional LES even in phases of LES relaxation and characterized by a missing propulsive peristaltic ("Aperistalsis"). Achalasia is the most common esophageal motility disorder. While there is a persistent hypertension of the LES in 50% only the missing relaxation is typical and characteristic. The pathologic cause of the achalasia is still controversially discussed in the literature. The diminished number of inhibitory ganglion cells within the esophageal wall is typically described by the pathologist.

The diagnostic workflow should include the esophagogastroduodenoscopy (EGD), a radiographic contrast imaging of the esophagus and the high-resolution manometry (HRM).

1. In EGD a dilatation of the esophagus, frequently accompanied by retained food or fluid is pathognomonic. The important diagnostic impact of EGD is the exclusion of other esophageal pathologies (tumors, strictures, eosinophilic esophagitis). Pseudoachalasia is defined as a bundle of disorders (e.g. sclerodermia) imitating classical achalasia by impairment of LES motility.
2. Radiographic contrast imaging of the esophagus typically shows the 'birds beak' sign caused by the proximal dilatation of the esophagus.

3. Esophageal manometry is the gold standard diagnostic tool for the functional evaluation of the LES: In contrast to the classical manometry typically consisting of 8 pressure sensors (4 inside the esophagus, 4 at the gastroesophageal junction), the high-resolution manometry [HRM] with a higher density of pressure sensors (every 1 cm normally) is used nowadays and provides a clear picture of the pressure changes during swallowing.

Achalasia should be classified according to the Chicago-Classification (V 3.0), which is based on the different results in HRM:

Type I: classic achalasia.
Type II: achalasia with panesophageal compression.
Type III: spasmic type.

This new functional classification gains more and more importance for clinicians providing a 'tailored' individualized therapeutic approach to a certain patient (e.g. surgical approach versus endoscopic myotomy [POEM]).

Pharmacological treatment of achalasia includes calciumchannel blockers and nitrates. Injections with botox, which prevent the release of acetylcholine at the terminal nerve endings have therapeutic effects for 6–9 months. Any pharmacologic therapy is less effective than endoscopic or surgical approaches. The same holds true for pneumatic dilatation, which achieves adequate short-time results, but fails to convince in the long run.

The Surgical Approach: The Cardiomyotomy (Heller)

The surgical principle of the functional treatment of patients with achalasia is still based on Heller's approach from 1913.

Nowadays most surgeons prefer laparoscopic surgery with 4–5 ports. The patient is positioned in a modified lithotomy and reverse Trendelenburg's position. Hereafter, a supraumbilical subxiphoidal (about one hand superior to the umbilicus) access into the peritoneal cavity is provided. The working ports are placed in the left upper quadrant laterally and in a subcostal left position. For liver retraction one additional port is placed at the right costal margin. A small 5 mm port should be positioned cranially on the right side of the epigastrium. In our hospital the operator is positioned between the legs, while the first assistant stands on the right (camera operator), the second to the left side of the patient.

After dissection of the phrenico-esophageal membrane and preparation of the diaphragmatic crura the circumferential preparation of the esophagus cranially to the mediastinum is performed as the next step. The mobilization of the esophagus allows a tension-free retraction of the esophagus into the abdominal cavity. The preparation of the anterior vagal nerve has to be performed carefully to avoid any injury. Once taken away from the anterior to the right side the vagal nerve is safe and the ventral myotomy is the next step. Myotomy is performed over the least 4–6 cm of the lower esophagus up to 2 cm to the proximal stomach. Most important pitfall is an incidental opening of the mucosa, which should be avoided! Up to now it is controversially discussed in the literature, if the incision should be extended into the sling fibers or to the clasp fibers (more at the right side) also. Classically the myotomy is "covered" by a partial fundoplication (Dor or Toupet procedure, see below), which is functionally relevant to avoid any postoperative GERD development.

The Thoracic Approach: Is There Still an Indication?

Treatment of diffuse esophageal spasm or spasmic type of esophageal achalasia (Type III) was the domain of the thoracic surgeon, due to the possibility to extent a long myotomy up to the high-thoracic esophagus. As shown in Fig. 1 a left-sided posterolateral thoracotomy (or thoracoscopy) is followed by an opening of the mediastinal pleura. The myotomy is performed over a long distance according to the segment of

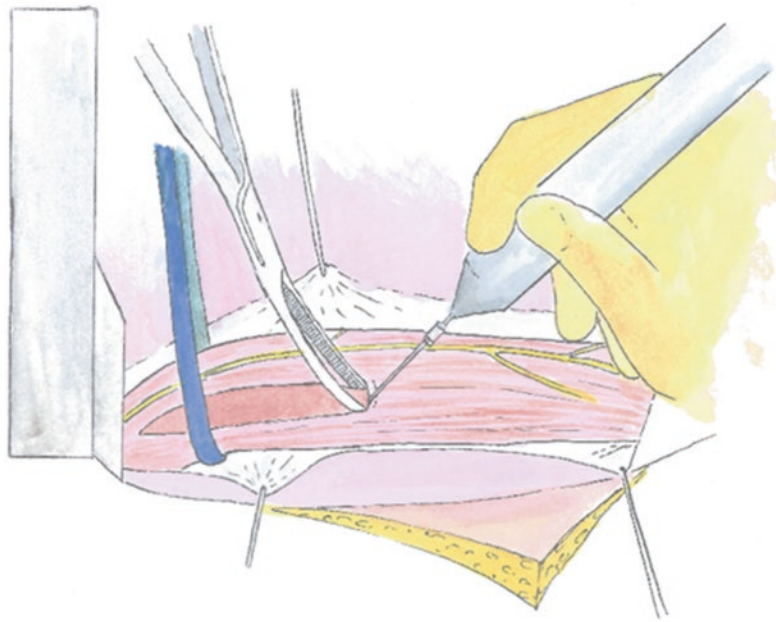

Fig. 1 In cases of a diffuse esophageal spasm the surgical myotomy over a long distance provided via a posterolateral left-sided thoracotomy is an easy and save therapeutic approach

spasmic musculature diagnosed in HRM prior to operation. As described for the laparoscopic Heller myotomy an anti-reflux technique is performed. For the thoracic approach the Belsey fundoplication (see Fig. 6) is preferred by most thoracic surgeons. Despite the advantage of a full-length myotomy the thoracic approach requires single-lung ventilation and insertion of a chest tube and is thus more challenging for the patients. Both the open and the thoracoscopic surgical technique could be replaced by the new endoscopic POEM approach in near future. Nevertheless the thoracic surgeon must know this operation technique as an escape strategy after POEM has failed.

Alternative Procedures and Evaluation/Comments

The peroral endoscopic myotomy procedure (POEM) is a rather young technique and was first introduced by Inoe et al. (Yokohama, Japan) [1] in 2010. Previously Pasricha and colleagues evaluated the new approach in an experimental pig model. Both the Heller and the POEM procedure are based on the myotomy of the same target muscles and thus on the same therapeutic principle. In contrast the approach to the target structures is different (Fig. 2): while during the laparoscopic Heller procedure the esophagus is prepared from an abdominal, transhiatal access (myotomy is performed in an oral direction) the POEM uses an endoscopic so-called 'mucosal entry' followed by an endoscopic submucosal dissection (the myotomy is performed in an aboral direction). One great potential advantage of the endoscopic POEM approach is the extension of the myotomy: during POEM procedure an extension of the myotomy both in the proximal and in the distal direction is feasible, which—in contrast—requires a thoracoscopy or thoracotomy, if classical Heller myotomy is not sufficient (e.g. in cases of spasmic motility disorders).

Both the Heller myotomy and the POEM procedure are very secure approaches. For both techniques complications like mucosa perforations have been described, which normally heal without any severe consequences. For

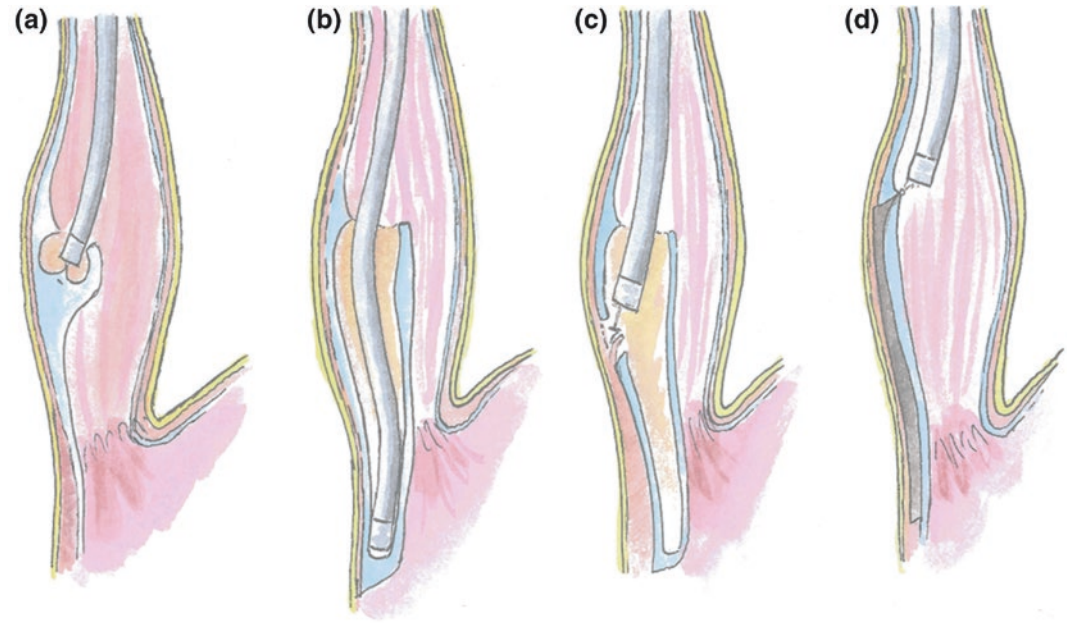

Fig. 2 The peroral endoscopic myotomy (POEM) procedure. After opening of the mucosa the submucosal plane is prepared (**a**). Hereafter preparations proceeds in a cranio-caudal direction (**b**). The myotomy is performed (**c**). The entry site is closed by endoscopic clipping (**d**)

Table 1 Comparison of peroral endoscopic myotomy (POEM) versus laparoscopic Heller myotomy (surgery) [2]

Author	POEM	Surgery	Study design	Outcome	Follow-up
Schneider et al. [3]	42	84	Retrospective	POEM safe, equal short-term results	6–12 months
Sanaka et al. [4]	36	142	Retrospective	Equal short-term results	2 months
Kumbhari et al. [5]	49	26	Retrospective	Equal results for achalasia type III	POEM: 8.6 months Surgery 21.5 months
Bhayani et al. [6]	37	64	Retrospective	Equal short-term results	1–6 months
Ujiki et al. [7]	18	21	Retrospective	Equal short-term results, less postintervential pain after POEM	POEM 4 months Surgery 5 months

the POEM an "intraoperative" bleeding could prohibit any further submucosal preparation, which thus could lead to a surgical escape strategy. In these cases the Heller myotomy (via an abdominal or thoracic approach) could serve as an rescue procedure "from the other side" of the muscle.

Due to the fact that the POEM procedure was introduced into clinical medicine recently, long-term results are still rare. Nevertheless the literature (and the evidence) of this new technique increased dramatically over the past years. Table 1 provides a summary on recent literature on the POEM procedure [2].

Recent literature reveals that both POEM and the Heller myotomy show:

- An adequate therapy of the symptoms.
- No difference concerning the clinical Achalasia scores (e.g. Eckardt score).
- No difference in procedure time.
- No difference in postprocedural pain.

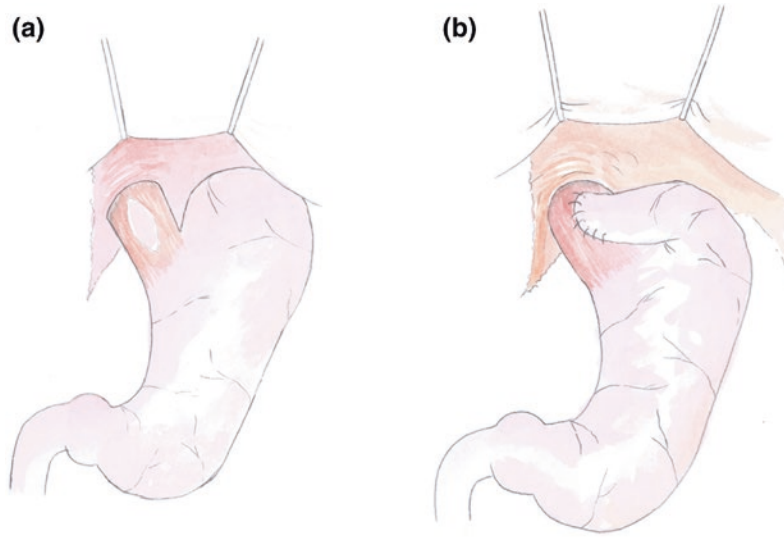

Fig. 3 Schematic drawing of the Heller myotomy. Myotomy is performed over the last 4–6 cm of the lower esophagus up to 2 cm to the proximal stomach. As an anti-reflux surgical procedure typically the Dor or Toupet fundoplication is performed. As shown in figure **b** the Dor procedure is a 180–200-degree anterior semifundoplicatio, while Toupet is a 270-degree posterior wrap

The rate of reflux might be increased after POEM procedure (20–30%) (whereas Heller myotomy is combined with an anti-reflux fundoplication!) [8].

In summary the Heller myotomy is still the therapeutic gold standard for patients with achalasia. The POEM procedure is a secure and rational alternative approach. Long-term results of POEM are still scarce and results of the prospective randomized multicenter trial POEM versus Heller myotomy are not available so far. Especially for type III achalasia (spasmodic type) and similar long-distance hypercontractile esophageal dysmotilities the POEM is of advantage, while type I achalasia is routinely treated by Heller myotomy in our hospital. In cases of simultaneous hiatus hernia or epiphrenic diverticula Heller myotomy allows a synchronous repair of additional anatomic pathologies (Fig. 3).

Hiatus Hernia

Hiatus hernia (HH) is defined as a partial protrusion of the stomach into the lower mediastinum through the esophageal hiatus of the diaphragm. As typical for all hernia the HH is accompanied by a epiphrenic hernia sac. Probably the prevalence in the western world is high and ranges between 30 and 50%! Typically there is a coincidence between the HH and the clinically symptoms of GERD. As published by Fuchs et al. recently a HH is coincident in 80–90% of the patients with GERD [9]. The other way round only 60% of the patients with HH suffer from GERD.

The most common classification world-wide differentiates between four different types of hiatus hernia [9, 10]

Type I: classical HH (migration of the GEJ and proximal stomach into the mediastinum [80–90%].

Type II: paraesophageal Hernia (GEJ remains inferior to the diaphragm, the gastric fundus/corpus migrates into the mediastinum) (Fig. 4).

Type III: combination of type I and type II (GEJ migrates superior to the diaphragm AND the proximal part of the stomach migrates along the esophagus to the mediastinum).

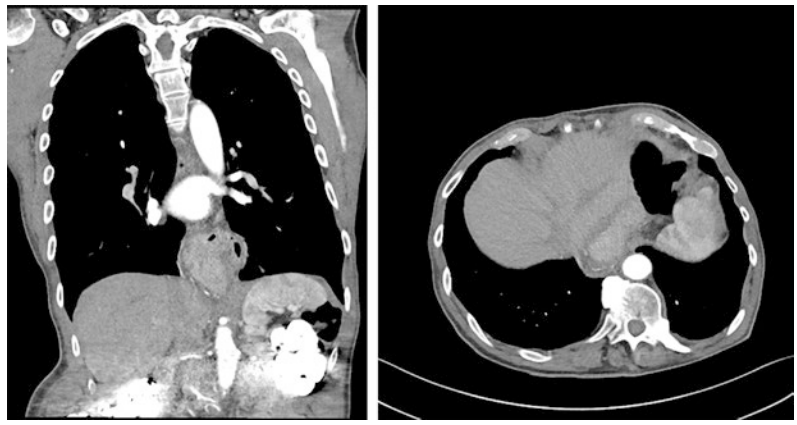

Fig. 4 Coronar and axial layers from a patient with a paraesophageal hernia. In contrast to axial hernia the paraesophageal hernia is characterized by a "real" hernia sac and a risk for incarceration

Type IV: large hernia with migration of other organs like colon, small intestine or spleen.

It is essential for the surgeon to differentiate between the classical or sliding HH (Type I) and the paraesophageal hernia (Type II), which bears the small but relevant risk of fatale strangulation and incarceration [11]. Due to this risk it is an accepted agreement that any symptomatic or asymptomatic paraesophageal hernia, should be surgically corrected. A conservative treatment is one option for elderly patients without any symptoms, but should be critically discussed in interdisciplinary rounds. Laparoscopic surgery is the gold standard for anti-reflux surgery including the repositioning of the axial hernia and crural adaption, but also is the standard approach for the treatment of paraesophageal hernia. For paraesophageal hernia the reposition of the viscera out of the chest into the peritoneal cavity is the first surgical step, followed by the resection of the hernia sac. One essential step for both anti-reflux surgery and the correction of the paraesophageal hernia is the reposition of the GEJ to an infradiaphragmatic position. To prevent any recurrent hernia a mobilization of the distal esophagus is necessary. Thus an intraabdominal tension-free distal esophagus of about 3 cm is ensured. Hereafter the esophageal hiatus is reconstructed as described below.

For the repair of paraesophageal hernia two important escape strategies are important for every experienced surgeon: If laparoscopy fails, either an open abdominal access or a left-sided thoracotomy are indicated. Usually a conversion to open abdominal surgery does not make a repair more feasible [11]. In contrast a thoracic approach might be very helpful: After single-lung ventilation the patient, who is placed in a right-sided lateral decubitus position, undergoes a left-sided posterolateral thoracotomy. Hereafter the hernia sac is circumferentially mobilized. After incision of the hernia sac and reposition of its contents the sac is excised. Hereafter the reconstruction of the crura followed by a 270-degree anterior Belsey-Mark IV fundoplication is performed. This technique is described in detail below. While about 90% are asymptomatic after surgical correction more than 30% show any sign of recurrence in radiographic imaging [11].

In contrast surgical correction of a sliding hiatus hernia is to control gastroesophageal reflux (see the section "GERD" below). Independent from the intended improval of the LES function every laparoscopic anti-reflux technique should be accompanied by a closure/adaption of the diaphragmic crura and a removal of the hiatus hernia. This is strongly recommended by the SAGES (Society of

American Gastrointestinal and Endoscopic Surgeons) and the EAES (European Association for Endoscopic Surgery) [9]. Depending on the size of the so-called 'hiatal surface area' (HAS), which can be calculated as published by Granderath et al., an additional implantation of a mesh should be performed [12].

GERD

Any anti-reflux barrier between the esophagus and the stomach requires an adequate physiological function of all anatomic structures, whose interaction forms the LES function. This contains a coordinated motor function of the esophagus with coordinated contraction and relaxation, the esophagophrenic and gastrophrenic ligaments and both the LES and the phrenic crura. Once one single structure is damaged or dysfunctional an incompetent anti-reflux barrier results.

Consequently acid or alkaline gastric content refluxes back into the esophagus. Over the last years the prevalence of GERD constantly increased. About 20% of the adults from the western world suffer from symptoms of GERD at least once a week. While first therapeutic steps contain life-style modifications and pharmacologic therapy (protone pump inhibitors, PPIs), surgery in contrast provides a causative therapy by anatomic repair of the anti-reflux barrier [13].

Modern literature reveals that despite several side effects like chronic kidney disease, Vitamin B 12 deficiency, hypomagnesiemia, osteoporosis, diarrhea, potential cardiovascular effects etc. the beneficial effects of PPIs predominate for patients with GERD. The indication for surgical therapy requires a detailed analysis of the characteristics of reflux disease and a proper patient selection.

Anti-reflux surgery remains the therapeutic gold standard for patients, who

(a) do not respond to PPI pharmacomedication.
(b) suffer from non-acid high-volume reflux.
(c) do not wish a long-term PPI therapy.

As ruled out above upper GI endoscopy is an important tool to identify a hiatal hernia or complications of GERD like esophagitis, Barrett's esophagus or cancer. Esophagitis is classified according to the Los Angeles Classification [14] (Table 2).

Patients suffering from GERD should undergo a 24-hour pH assessment of the esophagus. Hereby the episodes of acid reflux can be analyzed in detail concerning their frequency and duration. Due to the principle of this method the patients with non-acid reflux are, of course, not detected.

All patients with typical reflux symptoms should undergo a pH assessment, besides those patients, who have typical symptoms of reflux, endoscopic and histological evidence of an esophagitis and an adequate response to PPIs. Typical pitfalls of pH measurement are probe displacements, which could be avoided by a correct placement of the pH probe 5 cm above the upper border of the LES (determined by manometry). Patients have to stop H2-blockers for 3 days and PPIs 14 days before testing. For patients, who cannot stop taking PPIs or who suffer from non-acid reflux impedance measurement of the esophagus is an important additional

Table 2 Los Angeles classification of esophagitis according to the endoscopic findings

Grading	Endoscopic findings
A	One (or more) mucosal break $\leq$5 mm long that does not extend between the tops of two mucosal folds
B	One (or more) mucosal break $\geq$5 mm long that does not extend between the tops of two mucosal folds
C	One (or more) mucosal break that is continuous between the tops of $\geq$2 mucosal folds but involve less than 75% of the circumference
D	One (or more) mucosal break which involves at least 75% of the esophageal circumference

diagnostic tool for the preoperative evaluation of the disease. By a catheter system with multiple electrodes any change in impedance enables to determine the direction of the transport of a bolus inside the esophageal tube and thus to realize any reflux of a bolus back into the esophagus.

The manometry of the esophagus monitors the muscle tone of the LES (length, duration and pressure), which is changed in "classical" reflux disease, but furthermore detects patients with primary motility disorders like achalasia or sclerodermia, who suffer from reflux. Furthermore the degree of reflux and dismotility of the gastroesophageal junction is graded, evaluated and thus influences the decision of the surgeon concerning his fundoplication option (360 degree wrap [Nissen fundoplication] versus 270 degree wrap [Toupet fundoplication]).

Operation Technique—Fundoplication

A bundle of surgical techniques exists to perform antireflux surgery (Table 3). While the laparoscopic approach is the routine technique transthoracic or open abdominal approaches are reserved for patients undergoing redo surgery, multiple previous operations in the patient's history or strong contraindication against a capnoperitoneum (e.g. severe cardiopulmonary disorders). Several trials clearly show that both the 270-degree wrap and the 360-degree fundoplication show comparable results and are highly effective techniques to treat GERD. In contrast to the 360-degree wrap the partial fundoplication might allow vomiting and could reduce the incidence of gas bloat syndrome, while the 360-degree wrap provides higher durability compared to partial fundoplication techniques.

The principle steps of the transabdominal laparoscopic fundoplication are the mobilization of the distal esophagus and of the gastric fundus, followed by a plication of the fundus around the lower esophagus. By this a "high-pressure" zone at the EGJ is formed, which increases the tone of the LES and forms a barrier against an elevated intragastric pressure.

First described by Nissen in 1956 this surgical approach was modified by several variations: While during classical Nissen procedure the minor gastric curvature is mobilized and the posterior wall of the fundus is wrapped around to the anterior wall of the fundus Rossetti (-Hell) modified the original operation by wrapping the anterior wall of the fundus around, which required less mobilization of the stomach. In all original approaches a ligation of the short gastric vessels is not necessarily performed [15]. This is in contrast to the modern "floppy" Nissen fundoplication, where the short gastric vessels are divided and the complete proximal stomach is mobilized. This allows a wrapping of the lateral stomach posteriorly around the esophagus to the anterolateral margin of the fundus.

The fundoplication itself includes a 3-6 cm long 360-degree wrap with functionally excellent results.

Table 3 Different kinds of anti-reflux fundoplication techniques

Operation technique	Kind of fundoplication/wrap
Partial fundoplication Belsey Mark IV	270-degree anterior (transthoracic)
Lateral semi-fundoplication Hill (esophagogastropexy)	90–180-degree lateral (transthoracic)
Nissen	360-degree
Dor	180–200-degree anterior
Thal	90-degree anterior
Toupet	270-degree posterior
Watson	120-degree anterolateral

The patient is positioned in a modified lithotomy and anti-Trendelenburg position. Typically, 5 trocars are needed to perform the operation minimally-invasively. Once the first trocar is placed superior of the umbilicus in the midline position (we prefer open surgical access in contrast to the Veress needle) the capnoperitoneum is inflated. Two further trocars are placed at the right and left epigastric/subcostal position. For liver retraction one further access is provided at the right lateral upper quadrant. The fifth trocar is positioned at a left lateral middle abdominal position. The placement of the trocars is critical and depending on the experience of the surgeon.

First step is the division of the gastrohepatic ligament. Any atypical (complete or accessory) left hepatic artery from the left gastric artery should be detected and be preserved. After this surgical step the right diaphragmatic crus is clearly identified and the phrenoesophageal ligament divided. At this step any deeper preparation might lead to an injury of the anterior vagal nerve, which should be clearly identified before further proceeding. After blunt preparation of the right crus the esophagus is dissected anteriorly to the left crus. Preparation of the left crus is typically hindered by fatty tissue in this area. At this point the ligation of the upper short gastric vessels may be necessary.

Hereafter, the preparation of a "posterior window" behind the esophagus is the next surgical step. As for the anterior esophageal wall the dissection of the soft tissue behind the esophagus endangers the posterior vagal nerve, which must be clearly identified. Some surgeons recommend the placement of a vesselloop around the esophagogastric junction to enable a retraction. Independently from that potential step the preparation to the caudal crural closure is the next one. If the intraabdominal portion of the esophagus is too short the so-called 'Collis gastroplasty' could be an important maneuver to enable the construction of a functional fundoplication. After a vertical gastric incision parallel to the left border of the esophagus the latter is lengthened effectively. By non-absorbable sutures the crura are adapted. Any narrowing of the hiatus should be avoided, because it can result in a dysphagia, which is refractory to endoscopic dilatation in the long term. As the second part of the operation the gastric fundus is guided behind the esophagus. The so-called 'shoeshine test' is performed, when the fundus is brought behind the esophagus to test the fundoplication for adequate tension and orientation. The remnants of the short gastric vessels line up and the fundus remain in its position after the grasper is released. By three non-absorbable suture the wrap is formed and fixed. The wrap should be positioned at the distal esophagus.

Typical pitfalls performing Nissen-Rosetti fundoplication are:

(a) Bleeding (e.g. from the short gastric vessels, spleen. Typically bleeding while preparing the right crus and the GEJ comes from branches from the left-sided gastric artery/vein).
(b) Short Esophagus (Chronic reflux leads to a shortening of the esophagus, which can be found in up to 10% of the patients. This state bears an increased risk for a slippage or mediastinal herniation).
(c) Esophageal/Gastric perforation (typically by thermal damage using surgical energy devices).

Dysphagia and the so-called 'Gas Bloat Syndrome' are the most common complications in the long-term postoperative phase. While dysphagia is commonly seen immediately after fundoplication symptoms should resolve over the postoperative phase. Any persistence that exerts 12 weeks should lead to further diagnostics consisting of radiographic imaging/barium swallow of the upper GI tract. Herein the position or any stenosis of the wrap can be evaluated. In contrast to the original Nissen fundoplication the incidence of the gas bloat syndrome with gastric air trapping leading to abdominal distension and pain decreased significantly since the so-called 'short and floppy' wrap had been routinely used as the "gold standard" method for surgeons. The Toupet fundoplication and its variations (e.g., Guarner, Lind) is the most common laparoscopic partial fundoplication technique. The

fundus is guided posteriorly from the esophagus to the right side. At the right anterior margin of the esophagus it is fixed by one row of sutures. On the left anterior aspect of the esophagus the medial side of the fundus is fixed by another row of sutures. Recent literature reveals that both 360-degree Nissen fundoplication and Toupet fundoplication lead to equal rates of long-term postoperative symptom control [16]. Nevertheless, there are some "typical indications" for a partial fundoplication, which are listed in the following:

- severe aerophagia
- insufficient gastric fundus (e.g. previous subtotal gastrectomy, tubular stomach)
- in association with Heller myotomy for achalasia.

In 2000 Chapman et al. published the first robotic Nissen fundoplication [17]. A recent meta-analysis of five randomized controlled trials (n = 160 patients) underlines an equivalence in conversion and complication rates between laparoscopic and robotic approach [18].

In principle all surgical anti-reflux techniques can also be performed by transthoracic approaches. Specific situations, when an open thoracic approach should be discussed are for patients with

- previous fundoplication(s) in the patient's history
- esophageal shortening (Barrett esophagus, esophageal stricture, large hiatal hernia). The thoracic approach allows maximal moblilzation of the esophageal tube
- a synchronous surgical operation in the chest
- massive obesity.

Nearly all different techniques for anti-reflux surgery can be performed from a thoracic approach, too [13]. Typically the left-sided posterolateral thoracotomy (6th intercostal space) is preferred due to the fact, that it allows a better overview on the dorsal lower mediastinum. Most surgeons prefer to mobilize the distal intrathoracic esophagus first. After opening of the diaphragm by a circumferential incision 3 cm from the chest wall the mobilization of the esophagus is extended to the abdomen. Care has to be taken to avoid any injury of the vagal branches. If the mobilization is continued cranially it could be necessary to divide bronchial branches of the vagus. Due to the fact that the thoracic approach is typically chosen for patients with a migration of a previous fundoplication into the chest or for patients with a shortening of the esophagus an extensive mobilization of the esophagus could also require ligation of several esophageal branches from the aorta. Due to the intrinsic arterial plexus an adequate blood supply is still warranted. After this mobilization an infradiaphragmic reposition of the newly formed wrap is possible. To separate the cardia from the esophageal hiatus could be difficult. Some surgeons recommend an extension of the hiatus by a longitudinal incision though the central tendon even. Dissection of the phrenoesophageal membrane opens the view into the abdominal cavity and allows the circumferential mobilization of the cardia from the diaphragm. In cases of a hiatus hernia these steps are typically simplified. The luxation of the cardia into the thoracic cavity allows dissection of both the hepatogastric ligament on the right and the ligation of the short gastric vessels on the left side. After retraction of the mobilized esophagus and the gastric fundus anteriorly an approximation of the crura is feasible. The latter is performed by non-absorbable sutures, which are not tied at this timepoint. Typically 3–4 sutures are necessary, but must not lead to any narrowing of the esophageal lumen. The fundoplication is performed depending from the aspired kind of wrap (Table 3 and Fig. 5).

The **Belsey Mark IV procedure** (Fig. 6) is one classic transthoracic approach to perform a partial fundoplication [13]: Here the fundus is plicated around the anterior two thirds of the lower esophagus. Two rows of three seromuscular equidistant horizontal mattress sutures are placed between the stomach and the esophagus (1st row: 1.5 cm kranial of the cardia, second row: 2 cm above the first row). By the three sutures per row a 270-degree anterolateral

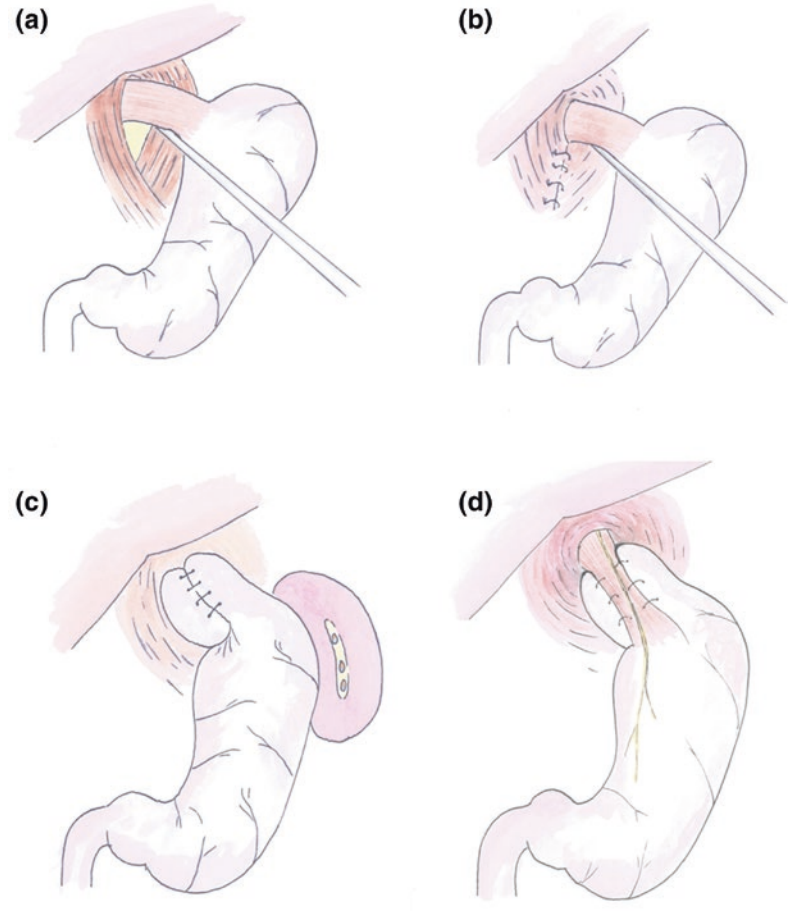

Fig. 5 Principles of (laparoscopic) anti-reflux surgery (**a**). Any hiatal hernia should be repositioned followed by crural adaption (**b**). Hereafter for example a 360° Nissen (**c**) or a 270° Toupet (**d**) fundoplication could be performed. Both fundoplication techniques lead to equal rates of reflux control

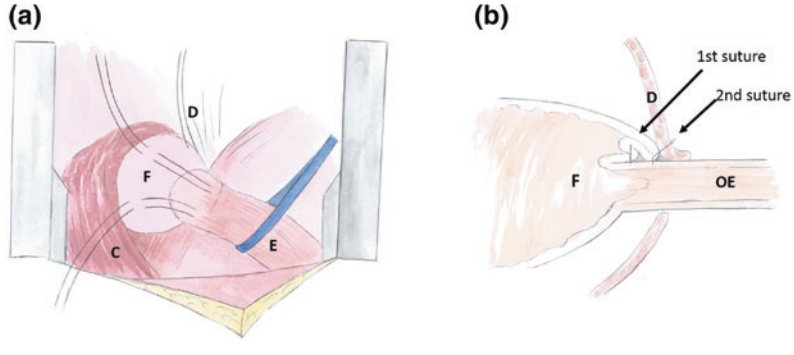

Fig. 6 **a** The principle of the Belsey-Mark IV approach is to form an anterolateral wrap by two rows of sutures: **b** After adaption of the crura (**c**) the gastric fundus (**f**) is grasped and shifted cranially to the anterolateral esphagus (**e**). With the second suture the wrap is additionally fixed at the diaphragm (**d**) to avoid any slippage of the wrap to the chest

fundoplication should be achieved. Due to the kind of surgical approach by a left-sided posterolateral thoracotomy the right-sided stiches typically require a rotation of the oesphagus. The second row furthermore serves as a fixation of the wrap at the thoracoabdominal border. This is achieved by a second stich of the three sutures through the diaphragm at the right-lateral, anterior and left-lateral site of the hiatus. By loosening the sutures at the gastric cardia the wrap can be digitally pulled back into the peritoneal cavity. The crural sutures are tied and the wrap is fixed at the hiatus.

The Belsey Mark IV procedure is recommended for patients, who fulfill the above-mentioned criteria for a transthoracic approach, and furthermore show a shortened esphagus during the operation. In this case the Belsey partial fundoplication (or the so-called 'Collis gastroplasty') could be good alternatives.

The Nissen fundoplication is the most important alternative transthoracic method to construct a wrap as anti-reflux procedure. The technique of fundoplication corresponds to the abdominal/laparoscopic approach and was described above. It should be the transthoracic surgical approach of the first choice for patients with an adequate length and a normal motility of the esophagus.

Conclusions/Summary

Functional surgery for the treatment of upper GI motility disorders requires a detailed knowledge on anatomy and physiology of the lower esophagus sphincter. Nowadays therapy of all dysfunctions is based on the three columns pharmacotherapy, endoscopic intervention and surgery. Surgery is typically performed from an abdominal/laparoscopic access. Nevertheless the thoracic surgeon plays an important role for functional surgery of the esophagogastric junction. He must be aware of the thoracic approaches to this challenging anatomical region, their indications and pitfalls. So doing, the thoracic surgeon plays a key role in the interdisciplinary discussions of cases with complicated functional disorders of the upper GI tract.

Self-study

1. Achalasia:
   a. requires surgery as the only therapeutic option.
   b. Is classified according to the Chicago classification.
   c. could be treated with the POEM procedure independent from the achalasia subtype.
   d. should be routinely treated by a thoracic approach and a Mark-Belsey IV procedure.
2. The thoracic approach for the treatment of the gastroesophageal reflux disease
   a. is routinely performed via an anterolateral thoracotomy.
   b. could be indicated in cases of previous abdominal fundoplications.
   c. should be combined with a myotomy
   d. should be performed via a right-sided posterolateral thoracotomy.

Answers

1. Achalasia:
   a. requires surgery as the only therapeutic option.
   b. is classified according to the Chicago classification. CORRECT
   c. could be treated with the POEM procedure independent from the achalasia subtype.
   d. should be routinely treated by a thoracic approach and a Mark-Belsey IV procedure.
2. The thoracic approach for the treatment of the gastroesophageal reflux disease
   a. is routinely performed via an anterolateral thoracotomy.
   b. could be indicated in cases of previous abdominal fundoplications. CORRECT
   c. should be combined with a myotomy
   d. should be performed via a right-sided posterolateral thoracotomy.

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Approaches and Surgical Techniques for Hydatid Cyst of the Dome of the Liver

Yener Aydin, Recep Sade, Ayman Ahmed, and Atilla Eroglu

Key Points

- Liver Hydatid cyst disease is a common health problem seen in sheep raising communities worldwide caused by the Tapeworm Echinococcus granulosus.
- Abdominal pain, jaundice, biliary fistula, bronchial fistula, cough, hemoptysis and anaphylactic shock are among the common clinical presentations.
- Indirect hemagglutination and ELISA are highly sensitive screening tests, while Ultrasonography plays an important diagnostic and therapeutic role.
- Management options includes: Medical treatment, Percutaneous treatment (PAIR, Catheter treatment), Surgery (Conventional, Laparoscopic) and Observation. All these modalities can be used alone or in combinations and must be tailored according to patient condition.
- Transthoracic/transdiaphragmatic access is an optimal approach to liver dome cysts.

Introduction

Hydatid cyst disease is an important parasitic infection, seen in the rural agricultural communities of the developing countries. The most common form is the cystic echinococcosis that is caused by Echinococcus granulosus, while the rare form the alveolar echinococcosis is caused by Echinococcus multilocularis. Hydatid cyst disease is endemic in Pakistan, India, Chile, Brazil, North Africa, Bulgaria, Balkans, Greece and Turkey [1, 2]. Hydatid cyst disease is most frequently affecting the liver (50–80%), the lungs (10–40%), and in 4–25% of cases both the lung and liver are involved [1–3]. Management of hepatic hydatid cysts consists of medical treatment, percutaneous interventions-aspiration, conservative and radical surgical interventions. Furthermore, different intervention methods can be applied in the hydatid cysts located in the liver dome. As experience increases, the rate of minimally invasive procedures increases, but the most appropriate method of treatment is patient-specific treatment planning [4].

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Disease Formation and Life Cycle

The Echinococcus granulosus requires two hosts to complete its life cycle. The dogs and the other predatory carnivores that host the adult stage of the parasite are the definitive hosts. Whilst the sheep, goat-like herbivorous creatures are the intermediate hosts in which the eggs convert into larvae. In Echinococcus multilocularis foxes and wolves are the definitive hosts, and rodents are the intermediate hosts. The human being is an incidental intermediate host [2].

The disease is transmitted by fecal-oral route. Tapeworm eggs are excreted in feces of the definitive host. Contaminated water and food are ingested by the intermediate hosts. The Egg hatches by bile acids and digestive enzymes in the intestine of the intermediate hosts, and the resulting larva stays attached to the intestinal mucosa. The parasites that enter the mesenteric circulation reach the liver via portal system. The larvae are 25–30 μ in diameter. Most of them cannot pass the liver, because the liver sinusoid diameter is 30 μ. For this reason, hydatid cyst is most commonly developed in the liver. The larvae that passed through the sinusoids reach the lung via hepatic venous circulation, inferior vena cava, right heart, and pulmonary arteries. The diameter of the capillaries in the lung is reduced to 8 μ. The larvae reaching the lungs stick to the lung capillaries and complete their development in the lungs. The parasite may also reach the lung via the transdiaphragmatic pathway, the lymphatic route and the portocaval anastomosis [2, 3].

The larva turns into a cystic metacestode form in the infected organ. A fibrous layer (pericystic layer) containing endothelial cells, eosinophils, giant cells and rich in fibroblasts and capillaries are formed around the enlarged cyst. The cyst wall is made up of two layers, endocyst and exocyst. The protective outer layer of the mucopolysaccharide structure is called exocyst and the fertile inner layer from which the daughter vesicles and the scolexes are born is called endocyst. There is a clear, sterile but antigenic fluid in the cyst that is called hydatid fluid. Hydatid cysts that develop in human body are usually solitary and called primary cyst. The rupture of the primary cyst wall leads to the formation of secondary cysts near the daughter vesicles and scolexes, neighboring tissues or via blood to distant organs [3].

Clinical Findings

Hydatid cyst is usually asymptomatic unless complicated with infection or rupture. Diagnosis is often made incidentally during imaging procedures for other pathology or when cystic pressure symptoms develop. Symptoms may vary according to the organ affected, size of the cyst and presence or absence of cyst's complications. Patient may present with abdominal pain due to cyst growth and gastrointestinal compression or the cyst may become symptomatic when the complications developed. In hydatid disease of the liver, cyst continue to grow over time and fistula may develop with the neighboring organs such as biliary tree or lung. Accordingly dome of the liver cyst when it rupture can cause a Bronchial fistula, and patient may present with hemoptysis, expectoration of cyst containing material or bile tinged sputum, and cyst-related secondary infection may develop. When the cyst ruptures in the peritoneal cavity or the vascular system, it may cause anaphylaxis due to allergen content of the fluid [3, 4].

Laboratory and Serological Tests

Routine laboratory tests are usually normal at the time of diagnosis. Liver function tests may show an elevation of the liver enzymes and cholestasis specially when there is compression of the bile ducts. Leukocytosis is usually seen in cases with infected hydatid cysts. Eosinophilia is seen in 25% of patients and hypogammaglobinemia can be seen in about 30% of patients. More pronounced eosinophilia can be detected after cyst rupture or cyst fluid infiltration [5].

Serological tests can help in the diagnosis. Indirect hemagglutination and ELISA (enzyme-linked immunosorbent assay) have 90% sensitivity in the diagnosis of liver hydatid cyst [6]. However, serological tests may give false positive

results due to cross-reactions occurring in patients with cestode infections such as Echinococcus multilocularis and tenia solium, some helminthic diseases, malignancies, liver cirrhosis and positive Ant-P1 antibodies. Demonstration of antigen 5 by immunodiffusion and immunoelectrophoresis helps in diagnosis. Parasite-specific IgE or IgG4 is not useful for diagnosis. The negative serological tests do not allow precise exclusion of hydatid cyst disease [7].

Imaging

Liver Hydatid cysts can be visualized and evaluated by ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI). Ultrasonography is widely used because it is available, easy and cheap. Plain radiography may show calcification within the cyst but cannot detect non-calcified cysts. For this reason, it is not used for definitive diagnosis or evaluation.

In the evaluation of Liver Echinococcus cyst, the sensitivity of ultrasonography is 90–95% [8]. The most common finding on ultrasonography is an anechoic, smooth, round cyst that may be difficult to distinguish from a benign cyst (Fig. 1). Ultrasonography allows cysts to be classified as active, transitional or inactive based on biological activity. This classification affects the choice of treatment.

CT is the best method for determining the number, size, presence or absence of daughter vesicles, presence of calcification or rupture, and determining the anatomic location of cysts (Fig. 2). It also allows the detection

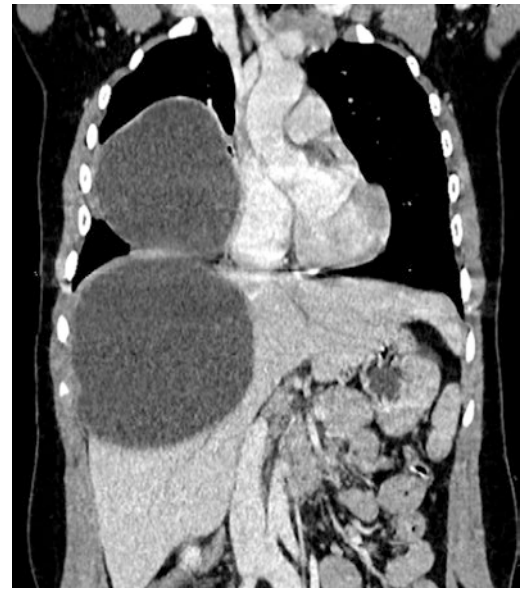

Fig. 2 A fourteen-year-old boy has the appearance of a massive hydatid cyst in the lower lobe of the right lung and in the liver dome

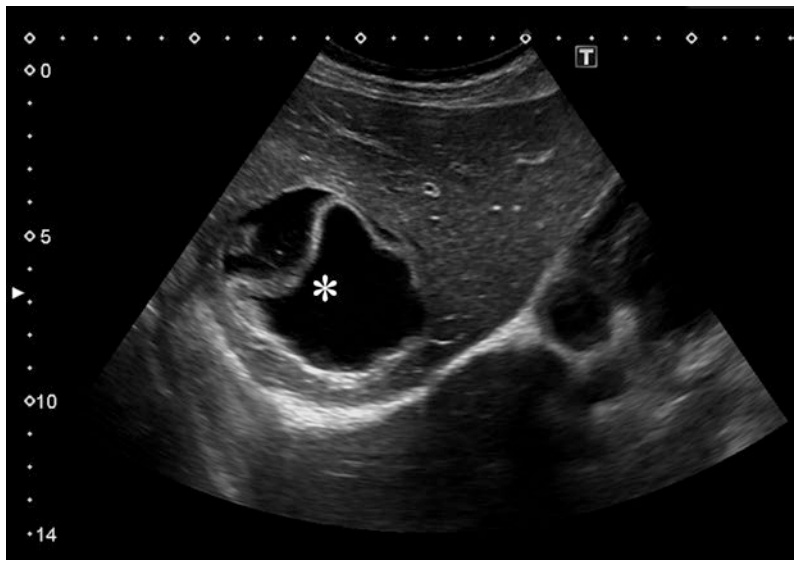

Fig. 1 A twenty-one-year-old man with type 3 hydatid cyst (asterisk) in the liver dome

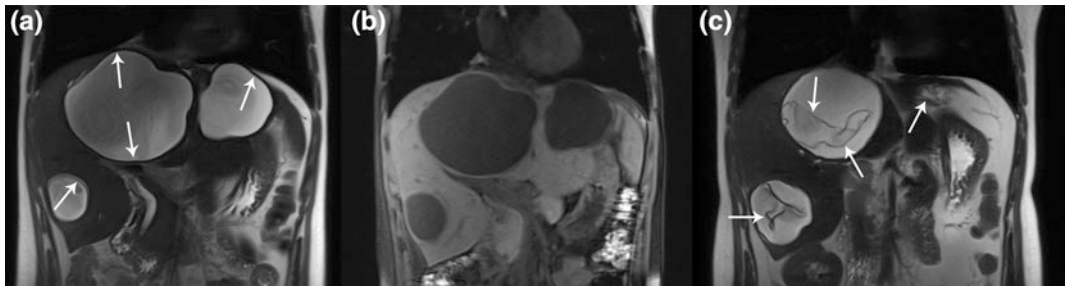

Fig. 3 Magnetic resonance images of thirty-year-old woman showed three type 1 hydatid cysts in the liver dome and right lobe of the liver. T2W (A) and contrast-enhanced T1W (B) images show thin walled (arrows) which is hypointense on T2W and unenhanced cysts. After medical treatment, there is cyst wall detachment (arrows) on T2W (C) image

Table 1 US characteristics, stages and treatment options of hydatid cysts according to WHO classification

WHO	US characteristics	Stage	Treatment option
CE1	Unilocular anechoic cystic lesion with double line sign	Active	Medical Treatment (<5 cm) Medical Treatment + PAIR (<5 cm)
CE 2	Multivesicular, multiseptated cysts, daughter cysts, rosette-like	Active	Medical Treatment + either modified catheterization or surgery
CE 3	Cyst with detached membranes	Transitional	Medical treatment + PAIR Or Medical treatment + either modified catheterization or surgery
CE 4	Heterogeneous cyst. No daughter cysts	Inactive	Observation
CE 5	Solid cyst with calcified wall	Inactive	Observation

US ultrasonography, *WHO* World Health Organization, *CE* cystic echinococcosis, *PAIR* puncture, aspiration, injection, reaspiration

of extrahepatic cysts. This is of paramount importance in the detection of right lung cysts with liver dome cysts. CT can also be used to monitor lesions and identify recurrences after treatment.

MRI has no significant advantage over CT for evaluation of abdominal or pulmonary hydatid cysts except in evaluating changes in intra- and extrahepatic venous systems. MRI may better describe the cyst capsule than CT and may be a better diagnostic tool for cysts, especially those associated with infection or biliary tracts affection (Fig. 3).

According to the World Health Organization (WHO) classification, liver hydatid cysts are divided into different groups according to type, number and size of the cyst (Table 1) [8, 9].

Treatment

Treatment includes antiparasitic agents such as albendazole, as well as, invasive interventions, ranging from percutaneous aspiration to radical resection. In recent years, in the treatmentof hydatid cyst, surgical interventions are directed towards minimally invasive techniques. Classical surgical approaches are increasingly been replaced by minimally invasive techniques such as percutaneous drainage procedures and laparoscopic approaches. No matter what technique is selected; the main goal of treatment is to prevent cyst progression, contamination of the abdominal cavity, cleaning the cystic content, and minimizing the cyst's cavity [8–11].

Medical Treatment

Medical treatment with scolicidal agents and prophylactic antibiotics should be started before and continued after surgery or percutaneous interventions. Benzimidazole derivatives (Mebendazole, Albendazole), are the most commonly used scolicidal agents, act by inhibiting the use of glucose by parasites and thus inhibiting ATP formation. Albendazole sulfoxide is given at a dose of 10 mg/kg/day divided into 2 doses for 28 days at 1–2-week intervals. Medical treatment is started 4–6 weeks before surgery/percutaneous intervention to decrease the risk of recurrence and complication and it is usually continued for 3–6 months according to cyst response. If there is a concomitant hydatid cyst in the lung, we prefer to start the medical treatment after surgery to prevent rupture of the lung cyst. If the cyst is not adequately responded to treatment, and no side effects developed, treatment may be extended to 12 months whether percutaneously treated or not. Abdominal pain, nausea-vomiting, pruritus, alopecia, redness, headache, rarely leukopenia, eosinophilia, jaundice, and slight elevation in transaminases may develop as a side effect of benzimidazole derivative drugs. In this case, it is advisable to reduce the dose or to extend cycle interval. All patients receiving medical treatment should be monitored with hemogram and biochemical tests before and after the procedure, especially liver enzymes since the side effects on liver functions are important [10, 11].

Percutaneous Treatment

Indications for percutaneous treatment in liver hydatid cysts include [17]: cysts according to the WHO classification CE1, CE2, CE3a and CE3b; recurrence or collection after surgery or percutaneous treatment; Inoperable and widespread disease; Presence of infected cyst-abscess formation; Pregnancy; patient who refuse surgery; Diseased or elderly patients who cannot tolerate surgical treatment or general anesthesia. Even if there are cross-sectional imaging methods to determine the percutaneous treatment of liver hydatid cysts and to determine the type of cyst, every patient should be evaluated with the US before the procedure.

Percutaneous treatment is most commonly performed under the US guidance. The location of the lesion, the internal structure of the lesion (membrane, solid component), the angle of entrance into the lesion, the parenchyma of the liver to be pierced, and the vascular-biliary structures in the entrance tract all are evaluated dynamically. During the procedure, cystography is performed by fluoroscopy and the cystic fistula is examined. In addition, in the complicated-thick-walled cysts, when the catheter is placed with the Seldinger technique, it is necessary to see the progression of the guide wire or catheter with fluoroscopy because of the risk of folding or coming out of the knuckle. In practice, when the diameter of the cyst is less than 5–6 cm, PAIR is used. If the diameter of the cyst is greater than 5–6 cm, catheter treatment and modified catheter techniques are used for complicated-infected cysts [10, 12].

PAIR

During the aspiration of the cystic content, a small amount of fluid is usually left behind to allow the needle to come out of the cyst, and then the scolicidal-sclerosing agent is administered. After waiting for about 10–15 minutes, reaspiration is done. Cyst aspiration, scolicidal-sclerosing agent administration and reaspiration procedures must be controlled with US guidance, especially when a fine needle such as 20 G is used since the needle has a risk of piercing the cyst and perforating the opposite wall. Sometimes it is difficult to distinguish simple liver cysts from hydatid cysts. The most reliable finding, in this case, is the detection of the germinative membrane during cyst aspiration [10, 12].

Catheter Treatment

Complicated cysts with large biliary leakage or infection are to be drained using 8–14 F Pigtail tipped and locked catheters. Catheter drainage

should be performed in cysts small as 4–5 cm in diameter especially when it is complicated or in post-operative collections if possible. After the catheter been inserted, free drainage is allowed, and cavity irrigation is performed. If the catheter is clogged, revision or catheter replacement is mandatory. Even if the drainage stopped, the catheter should be kept for at least 1 week, because of the risk of reopening of the cystic fistula especially in the centrally located large cysts. If the 24-hour drainage falls below 10 cm^3, cavitography is performed and if there is no fistula, sclerosis is performed, and the catheter is withdrawn [11].

Modified Catheterization Treatment

It is made using wider catheters (10–14 F) to completely drain the cyst contents. After the contents have been drained, cystography and daily irrigation must be repeated. Other procedural steps are the same as standard catheter therapy [11].

Surgical Treatment

Surgical treatment was the primary therapeutic modality for echinococcal cystic disease of the liver before the invention of the percutaneous approaches. Today, surgery continues to be the gold standard treatment for larger complex cysts. Indications for surgical treatment in liver hydatid cysts are: stage CE2–CE3b Cysts according to the WHO classification; large-sized; superficially located liver cysts (high risk of spontaneous rupture, percutaneous intervention is not appropriate); septic; secondary infection with daughter vesicles; cysts with bilateral opening or with compression of peripheral organs [13].

The basic curative approach in disease treatment is invasive open surgical interventions. However, in parallel with technological developments, minimally invasive procedures have begun to be used safely and effectively in the treatment of hepatic hydatid cyst. Rapid treatment can be achieved with a radical surgery, but post-intervention morbidity can be up to 60% and mortality up to 7.5% [14]. Surgical procedures are generally not recommended in small-sized, asymptomatic cysts and patients with poor overall performance.

The main treatment of liver hydatid cysts is surgical. The aim of surgery is to completely remove the parasites in a way that protects the liver functions, sterilization of the cyst content, and removal of the germinative membrane. Surgical techniques such as partial cystectomy, capitonnage, marsupialization, partial liver resection or lobectomy can be applied. Although radical methods reduce bile leakage and post-operative recurrence rates, they are usually not performed in areas where the disease is endemic due to the high intraoperative risks and the risk of recurrence of cysts in the remaining liver [15]. In addition, surgical procedures such as marsupialization and internal drainage are now abandoned due to high complication rates. The surgical technique to be applied may vary from patient to patient depending on the number of cysts, size, localization, the presence of infection, and whether complications are there.

Surgical procedures are either conservative or radical. In radical procedures, the cyst is completely removed, but residual cyst cavity remains in conservative interventions. Conservative "unroofing" and drainage operations are preferred and more frequently performed in liver hydatid cyst, whilst radical resections are performed in selected and smaller number of patients. However, more intraoperative complications develop in radical procedures [16].

Aspiration of the cyst content is to be performed during the surgical procedure, and scolicidal agent is to be injected into the cyst and aspirated. 15–20% hypertonic saline, 70–95% ethanol, 5% cetrimide is used as scolicidal agents [17]. During the procedure, attention should be paid to the risk of anaphylactic shock and secondary hydatidosis due to contamination of the peritoneal cavity with cyst fluid. Surgery is aimed at making the residual cyst cavity as small as possible. Seroma, secondary bacterial infection, and abscess formation may occur in

the residual cavity after surgical intervention. In such cases, diagnostic difficulties may arise during the patient's follow-up as it might be mistaken for disease recurrence. Methods such as marsupialization and omentoplasty can be applied to minimize cavitation [17].

The right thoracoabdominal incision, subcostal incision, right paramedian incision or right posterolateral thoracotomy can all be used to access the liver dome cysts. Kouraklis et al. [18] revealed that thoracoabdominal, right subcostal or paramedian incision is associated with higher morbidity than thoracotomy alone. The thoracoabdominal approach for hepatic hydatid disease is indicated in patients with hepatopulmonary extensions or in large cysts adherent to the vena cava or suprahepatic veins. This is the most common method used in cystic cases of the right lung. However, right lateral thoracotomy provides a better exploration of liver dome cysts, even if there is no hydatid cyst in the right lung. Thus, partial cystectomy or total pericystectomy is technically easier to perform. This approach has a lower morbidity and mortality than the thoracoabdominal approach, especially for elderly patients and patients with poor overall performance.

Transthoracic Approach to Hydatid Cysts in the Liver Dome

Transthoracic approach to hydatid cysts in the liver dome is a popular technique. A single-seated transthoracic approach protects the patient from a second operation or invasive procedure, especially in those cases where the right lung is involved. According to the cyst localization in the lungs, these cases are approached-via thoracotomy through the 6th, 7th or 8th intercostal space. First, surgical treatment is applied to the lung cyst. We prefer cystotomy and capitonnage for these pulmonary cysts as a standard. Then the diaphragm is opened with a radial incision over the area where the liver cyst is palpated. The cyst fluid is aspirated, and the cyst membrane is removed. In lung and liver cysts, we prefer to wash the cyst cavity with saline and clean it with povidone-iodine soaked sponges. The biliary leak is checked, and leakage places are sutured. If there is a giant cyst, it may be preferable to fill the cavity with omentum. In smaller cysts, the cyst cavity can be narrowed by sutures and thus the space is reduced. Before closing the diaphragm, a drain is placed over the cavity and drain is brought out through the abdominal wall (Fig. 4). The opening in the diaphragm is closed with nonabsorbable sutures. The chest drain is placed in the pleural cavity and the thoracotomy wound is closed. Percutaneous needle aspiration can be successfully applied in the treatment of uncomplicated hepatic hydatid cysts. The same concept of transdiaphragmatic needle aspiration of the liver cyst during right thoracotomy has been successfully applied in cases with concomitant right lung and liver hydatid cysts that saved the patients from a second surgery or interventional procedure. The feasibility of this method and its reasonable morbidity and reliability has been demonstrated in many studies [2, 4–7].

Even if there is no hydatid cyst in the lung, thoracotomy provides a better exposure than laparotomy for a hydatid cyst located in the liver dome. The resection of the liver cysts is basically like that of the lung cysts. However, there is a significant difference between the two operative techniques. Liver cysts contain more vesicles than lung cysts. Therefore, caution must be exercised to prevent the spread of living vesicles to the abdomen and chest. Before removal of the cyst, hypertonic saline solution or 10% povidone must be injected into the cyst via diaphragm to kill the parasite [2]. We routinely prevent the cysts from infecting the surrounding tissues by wrapping around the chest and abdominal cyst with sponges soaked with povidone iodine.

Laparoscopic Approach

Recently, the number of publications has been increased indicating that laparoscopic hydatid cystcyst surgery can be successfully applied in the treatment of this disease. It is stated that it can be applied safely in cysts with the peripheral

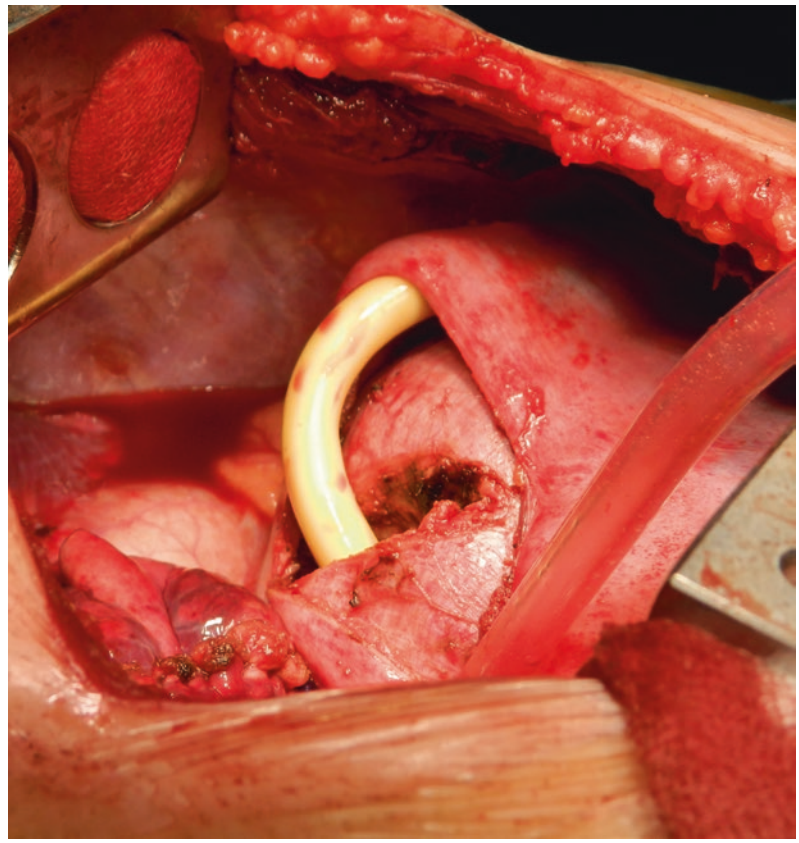

Fig. 4 Intraoperative view of a case with right lung and liver dome cyst is presented. The transthoracic approach shows a pezzer drain placed in the liver cystic cavity after simultaneous intervention in the lung and liver cyst

settlement, not very large, and with partial calcified walls [19].

There is no standard technique in the laparoscopic treatmentof hydatid cysts of the liver. Indications, how to prevent spillage of the cyst content, how to do an evacuation, and how to obliterate the residual cyst cavity will be discussed. Early stage, uncomplicated and noncalcified, peripherally located liver cysts are suitable for laparoscopic treatment. Whilst Central, thick, calcified or complicated cysts in the liver parenchyma are not suitable for laparoscopic treatment. There is also an access problem in posteriorly located cysts [20].

There is no consensus on the standard laparoscopic technique for liver hydatid cystcyst surgery. The methods that can be applied vary according to the size, the localization, the number of the cysts, the experience of the surgeon and the technical difficulties. Three or four port is enough for the intervention. During drainage and evacuation, special tubing is used beside disintegrator aspirator used in open surgery to prevent peritoneal spillage; trochlear drainage techniques that were introduced directly into the cannula or into the cyst [19, 20].

The laparoscopic approach has the advantages of faster recovery, shorter surgery time and length of hospitalization and lower costs when compared to conventional open surgery. However, safe access to the posterior/superior segmental cysts, liver dome cysts, and deep parenchymal cysts are difficult. With standard laparoscopic instruments, it is difficult to effectively drain all the components of the cyst. In addition, the risk of pouring cysts into the peritoneal cavity due to increased intraabdominal pressure due to pneumoperitoneum is slightly higher [7].

Result

Surgery is being used as a gold standard approach in almost all cases of liver hydatid cyst disease, while recent development of less invasive methods (PAIR) is the ideal tool in appropriate cases (CE1–CE3) because it is minimally invasive and reproducible. Laparoscopic surgical interventions have recently been successfully used. However, it may be difficult to reach the liver domehydatid cysts near the diaphragm atic surface by the abdominal approach, in such cases thoracotomy with transdiaphragmatic access to the liver dome cyst is a reliable and effective method of intervention, especially if there is a concomitant lung hydatid cyst. This method protects the patient from a second surgery or invasive procedure. Drug therapy in hepatic cysts can be used alone or as adjunct treatment in many cases to reduce the viability of the pre-interventional cyst and to prevent relapse.

Self-study

1. Surgical treatment for liver hydatid cysts is indicated in all of the following Except:
   (a) Cysts according to the WHO classification CE2–CE3b.
   (b) Small-sized cysts.
   (c) Secondary infection with daughter vesicles.
   (d) Cysts located superficially in liver.
2. All of the following are indications for percutaneous treatment in Liver hydatid cyst Except:
   (a) Inoperable and widespread disease.
   (b) Recurrence or collection after surgery or percutaneous treatment.
   (c) Biliary leakages.
   (d) Pregnancy.

Answers

1. Surgical treatment for liver hydatid cysts is indicated in all of the following Except:
   (a) Cysts according to the WHO classification CE2–CE3b.
   (b) Small-sized cysts—(**CORRECT**).
   (c) Secondary infection with daughter vesicles.
   (d) Cysts located superficially in liver.
2. All of the following are indications for percutaneous treatment in Liver hydatid cyst Except:
   (a) Inoperable and widespread disease.
   (b) Recurrence or collection after surgery or percutaneous treatment.
   (c) Biliary leakages (**CORRECT**).
   (d) Pregnancy.

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Approaches and Surgical Techniques for Retrocostoxiphoid Hernias

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Key Points

- The treatment for retrocostoxiphoid hernia is eminently surgical.
- The objectives are: dissection of the hernia sac, reduction of the herniated viscera, repair of associated lesions and closure of the diaphragmatic defect.
- Morgagni hernia always has a peritoneal sac.
- Surgical approach for retrocostoxiphoid hernia can be abdominal or thoracic, classic or mini-invasive.

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Definitions

Diaphragmatic hernia consists in the herniation of the abdominal structures in the thoracic cavity due to a defect in the diaphragm (Fig. 1) [1].

Retrocostoxiphoid hernias occur through the sternochondral triangles, also called Larrey spaces. They were first described in 1769 by Giovanni Battista Morgagni based on cadaver observation and thus these hernias have his name, in conjunction with Larrey who described a surgical approach to the pericardial sac through the same triangles [2–4]. ***Morgagni hernia*** occurs as a result of an anterior medial septum transversum defect due to the lack of fusion of the pars sternalis with the pars costalis of the diaphragm or as a failure of muscle tissue to spread to the area during embryologic development (Fig. 2) [2, 3, 5]. It appears mostly on the right side, despite protection from the liver, because the pericardial attachments protect the left hemidiaphragm from herniation by providing extra support to the weakened or absent muscle.

The retrocostoxiphoid hernia is the least common of the congenital diaphragmatic hernias (which occur in approximately 1 of 3000 live births) accounting only for 2–3% of cases (Fig. 3) [6–8].

Morgagni hernias can be encountered in any period of life including the prenatal one [9] but, despite their congenital etiology, they

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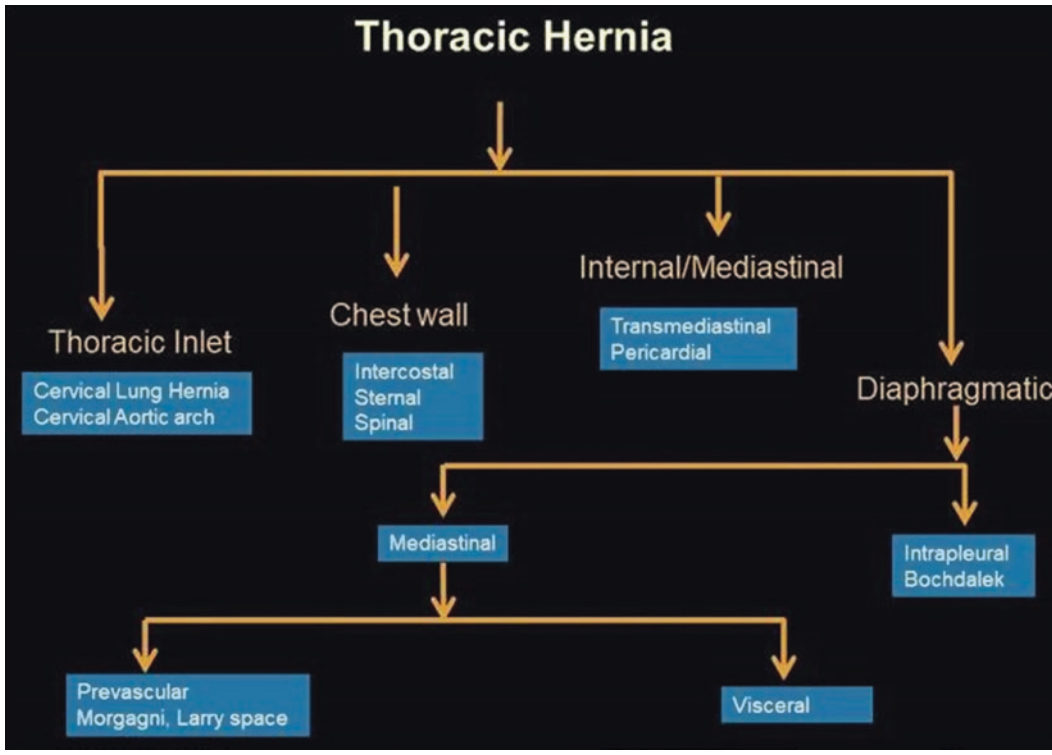

Fig. 1 Flowchart depicting the different types of thoracic hernias seen on imaging. From Ref. [1]

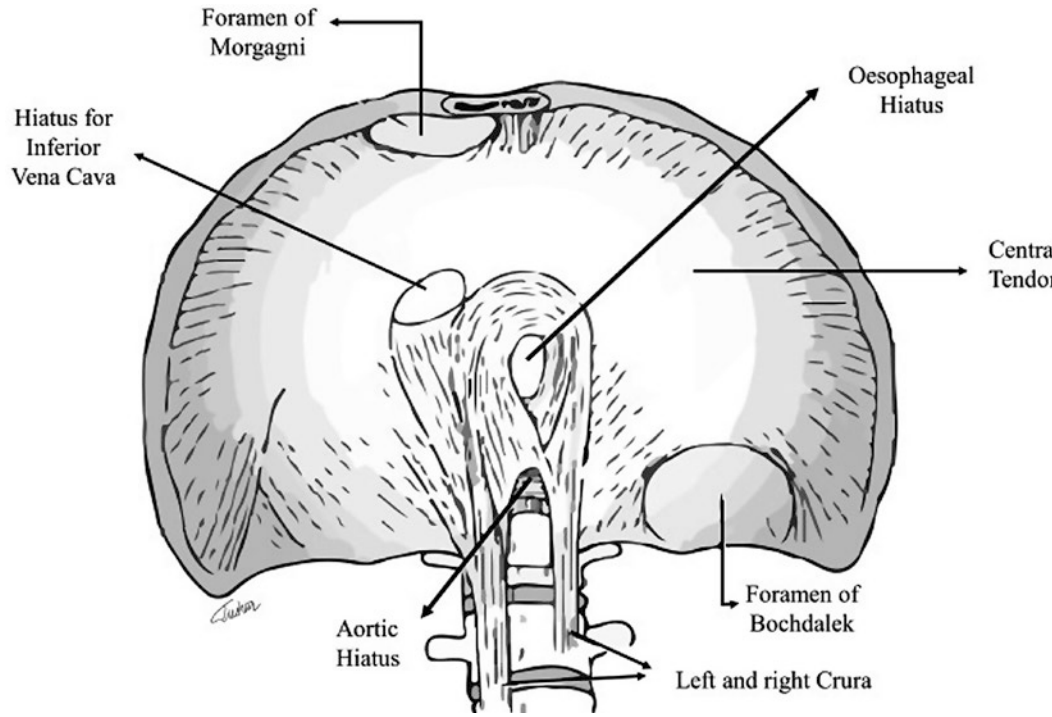

Fig. 2 Anatomy of the diaphragm (original illustration). From Ref. [5]

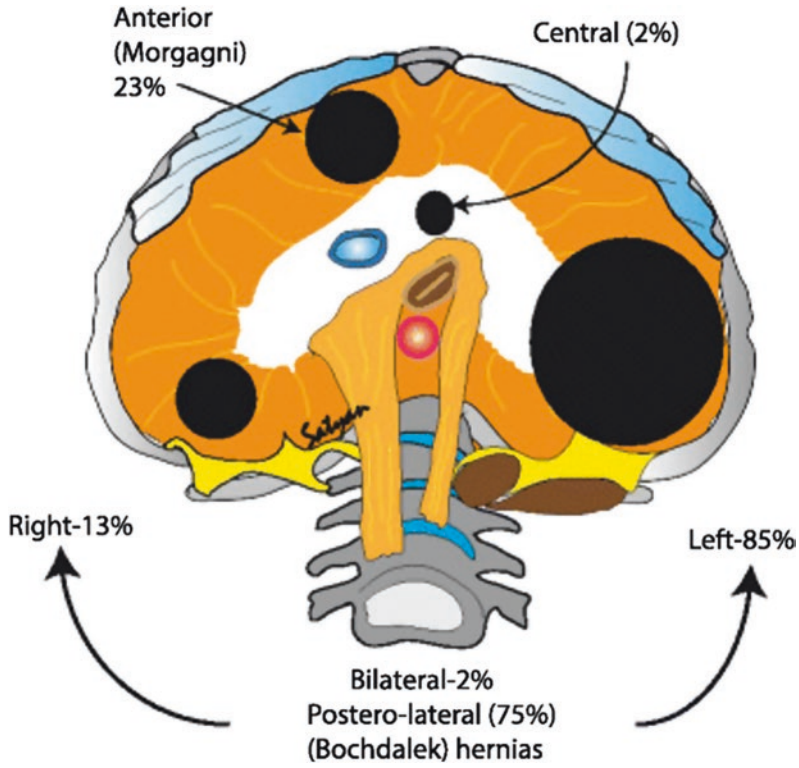

Fig. 3 Classification of congenital diaphragmatic hernia based on location of the diaphragmatic hernias: Most common type of hernias are the posterior lateral hernias (70–75%) also known as Bochdalek hernias, with majority occurring on the left side (85%) and less frequently on the right side (13%) or bilateral (2%). Other types of hernias are the anterior defects or Morgagni hernias (23–28%) followed by the rare central hernias (2–7%). (Copyright Satyan Lakshminrusimha). From Ref. [8]

are detected less frequently in children than in adults. The congenital defect tends to enlarge with age due to episodes of raised intraabdominal pressure, risk factors for this being obesity, pregnancy, abdominal trauma, COPD and chronic constipation [5, 10–12].

In the case of children, Morgagni hernias are diagnosed more readily in boys [13], a preponderance which reverses with adult age when they are more frequent in women [10, 14]. It can be associated with other anomalies such as: Down syndrome, Turner's syndrome, pentalogy of Cantrell, Noonan syndrome, Prader–Willi syndrome, ventricular septal defect, dextrocardia, scoliosis and others [10, 15–17]. Malformations are more often identified in children [18].

Typically, the hernias contain only omentum, but the transverse colon, small bowel, stomach or liver may also be implicated [11]. The presence of a hollowed viscus may lead to life-threatening complications such as acute obstruction, volvulus, or strangulation. The patients are usually asymptomatic and incidentally diagnosed during unrelated examinations [19]. Newborns may present with respiratory distress but more rarely than in other congenital diaphragmatic hernias [16]. Children commonly present with recurrent chest infection or failure to thrive [20]. Adults may present with abdominal symptoms: discomfort, pain, constipation, subocclusive syndrome or, more rarely, with thoracic symptoms such as dyspnea or palpitations [2, 3, 21, 22]. The rarity of the disease and

the vague symptoms may lead to delays in diagnosis and severe complications. The symptoms may come and go as the hernia content slides in and out of the defect [1].

On a **chest radiograph**, a Morgagni hernia appears as an opacity in the cardiophrenic angle, which may be homogenous if only the oment or liver are implicated or show a fluid-air level if a hollow viscus is present (Figs. 4 and 5) [23].

The radiography may be normal in intermittent herniation. Barium studies may be used to highlight visceral herniation (Fig. 6).

Ultrasound scans may evidentiate the presence of liver in the thorax [14, 15].

High-resolution CT is the gold standard in the imaging of Morgagni hernia. It can demonstrate the diaphragmatic defect and the organs that herniate through it (Figs. 7 and 8) [23].

The herniated fat appears continuous with the abdominal omentum, through the defect and the herniated organs are also easily identified. **MRI** can also be helpful in diagnosis but is usually not required [4, 24].

Treatment

The treatment for retrocostoxiphoid hernia is eminently surgical. The objectives are: dissection of the hernia sac, reduction of the herniated viscera, repair of associated lesions and closure of the diaphragmatic defect.

Surgical repair is indicated even in asymptomatic patients (Fig. 9) [23, 25], to prevent the onset of life threatening complications such as: hernia incarceration, bowel obstruction, strangulation, or gastric volvulus [5, 26]. The surgery is usually elective, emergency intervention being reserved to patients which present with acute complications [27]. Owning to the rarity

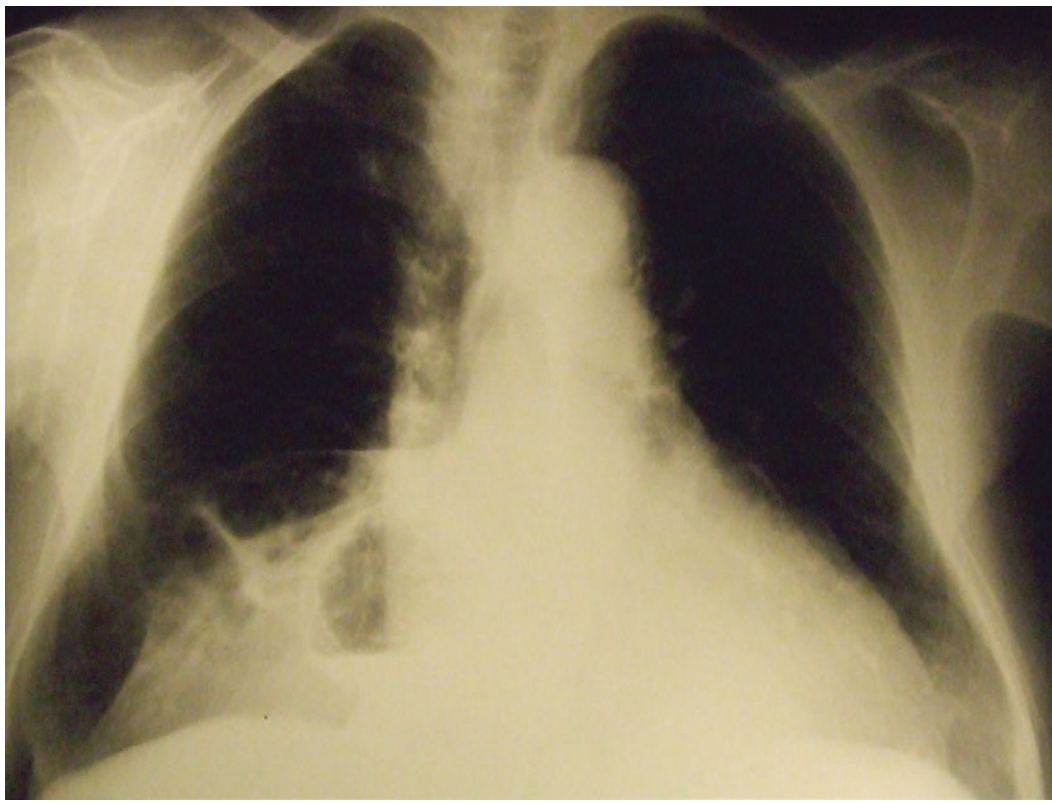

Fig. 4 Postero-anterior radiography—an inhomogeneous opacity with air–fluid levels located in the right costodiaphragmatic sinus (Morgagni hernia containing colon and gastric antrum)

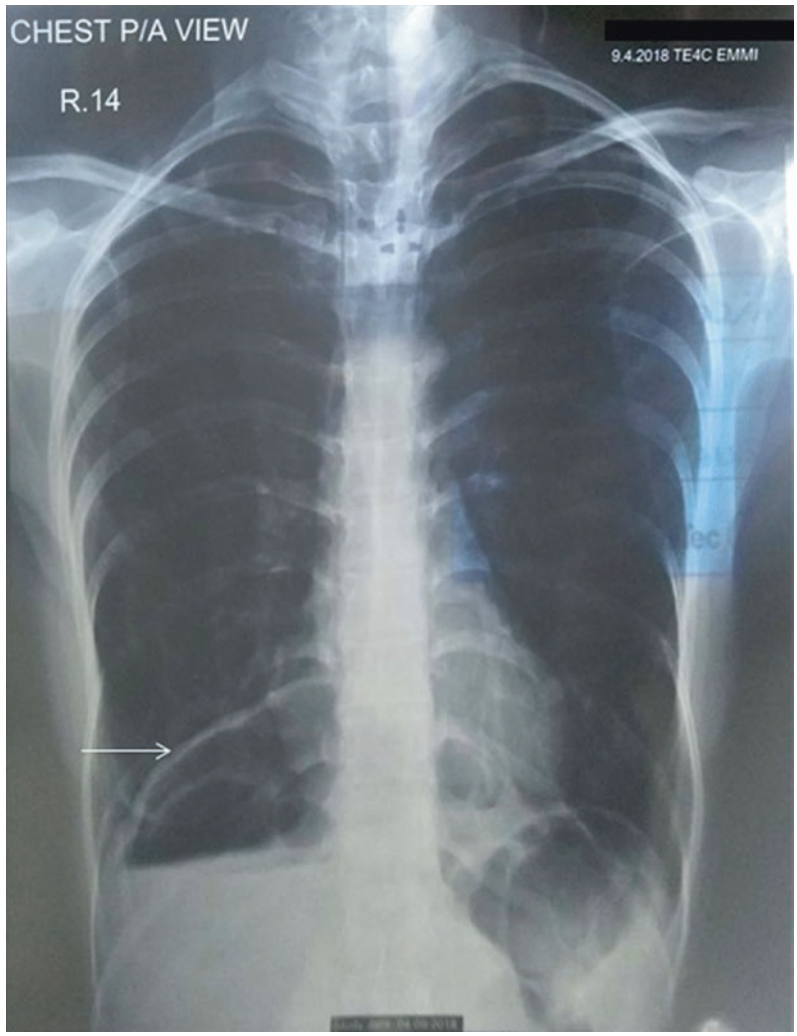

Fig. 5 Plain postero-anterior chest X-ray showing abnormal air fluid level (white arrow) in the right basal hemithorax above the diaphragm. From Ref. [23]

of Morgagni hernia there is no clear consensus on preference for operative repair technique [28, 29].

Surgical approaches can be abdominal or thoracic, classic or mini-invasive.

The abdominal approach is preferred because it has several advantages:

- easier reduction of the hernia contents;
- evaluation of the contralateral diaphragm (for bilateral hernias);
- treatment of associated diseases [30];
- easier treatment of complications.

Abdominal approach can be done by a xiphoombilical incision (the preferred one) or by a subcostal, or paramedian incision [4]. It is sometimes harder to excise the hernia sac through this last approach.

The ***thoracic approach*** is preferred in case of:

- uncertain diagnosis (a mediastinal tumour is suspected) [16]
- intrathoracic disease requiring surgical intervention
- recurrent cases or suspected dense adhesions between hernia contents and intrathoracic organs.

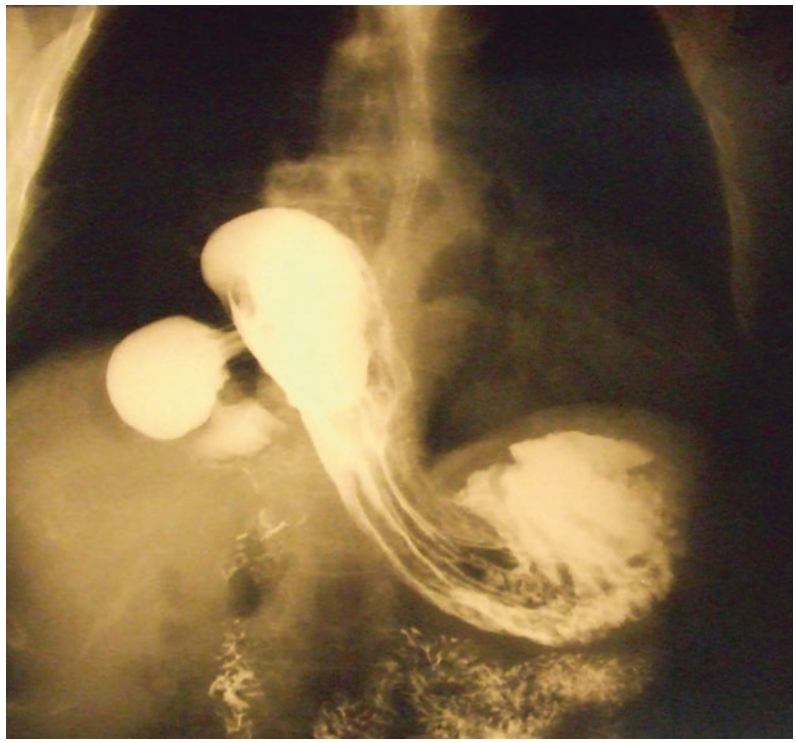

Fig. 6 Postero-anterior radiography of a barium-filled stomach partially herniated into the chest through a right-sided foramen of Morgagni hernia

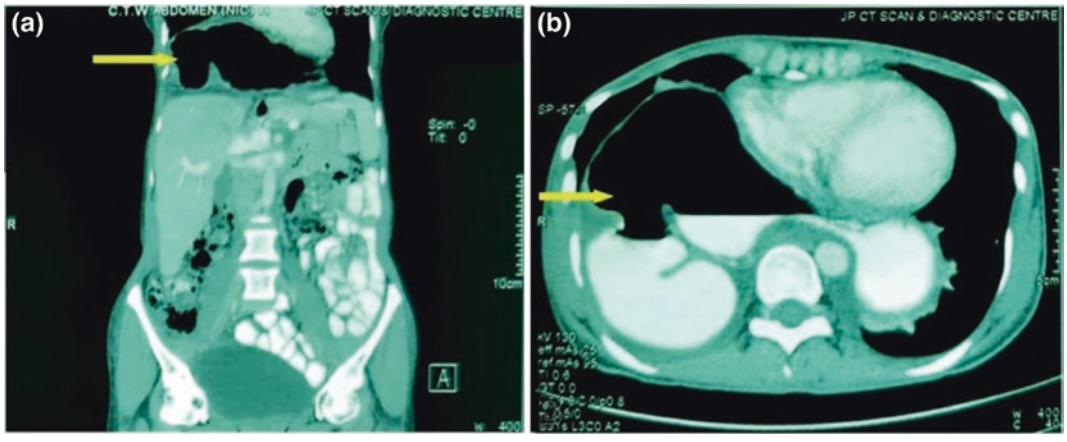

Fig. 7 Preoperative coronal (**a**) and axial (**b**) **computed tomography** slice showing gastric bubble (yellow arrow) indicating herniation of stomach into the thorax. From Ref. [23]

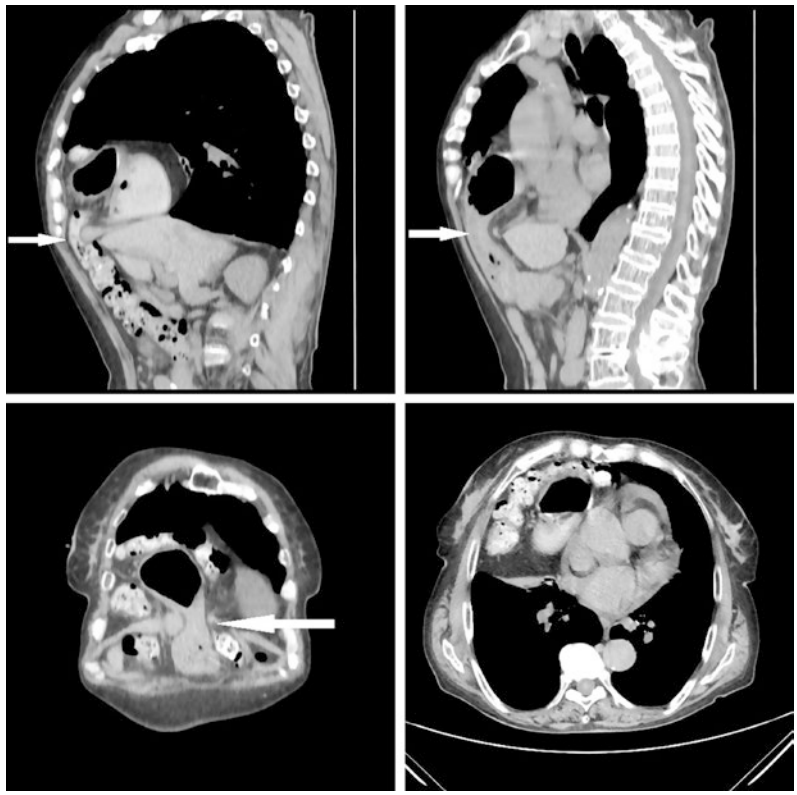

Fig. 8 CT scan with oral and intravenous contrast with axial and sagittal reconstruction show herniated stomach and transvers colon through an anterior defect in the diaphragm (white arrows)

It can be done by anterolateral thoracotomy. Trans-sternal repair may be used in patients undergoing concomitant open-heart surgery (Fig. 10) [2, 3, 31]. The thoracic approach does not permit the evaluation of bilateral forms and requires pleural drainage. Through this approach, it is, sometimes, very hard to reduce the hernia content.

This approach is usually selected based on the surgeon background and experience [32, 33].

The ***abdominal approach*** offers excellent visualization of the hernia and its contents (Fig. 11). The herniated organs must be repositioned in the abdominal cavity. This is generally easy because a Morgagni hernia always has a peritoneal sac [34] and there are few adhesions between the herniated organs and the sac [25]. Gentle pulling is usually enough to bring back the hernia contents in the abdominal cavity. Difficulties can arise in case of complications such as incarceration, gastric volvulus or strangulation and intestinal obstruction. Enlargement of the hernia ring may be necessary. Also when the distended stomach or bowel cannot be reduced a thoracotomy may be necessary, to allow bimanual manipulation to bring back the organs into the abdomen where resection may be performed if the viscus is compromised [4, 7].

The next step is to inspect the diaphragm and abdominal organs for associated malformations that may now be corrected (Fig. 12) [7, 34–36].

One thing to consider is the attitude versus the hernial sac (Fig. 13). It may be excised or it may be left in place [22]. Arguments for sac removal are: avoidance of fluid accumulation and formation of a mediastinal cyst, prevention

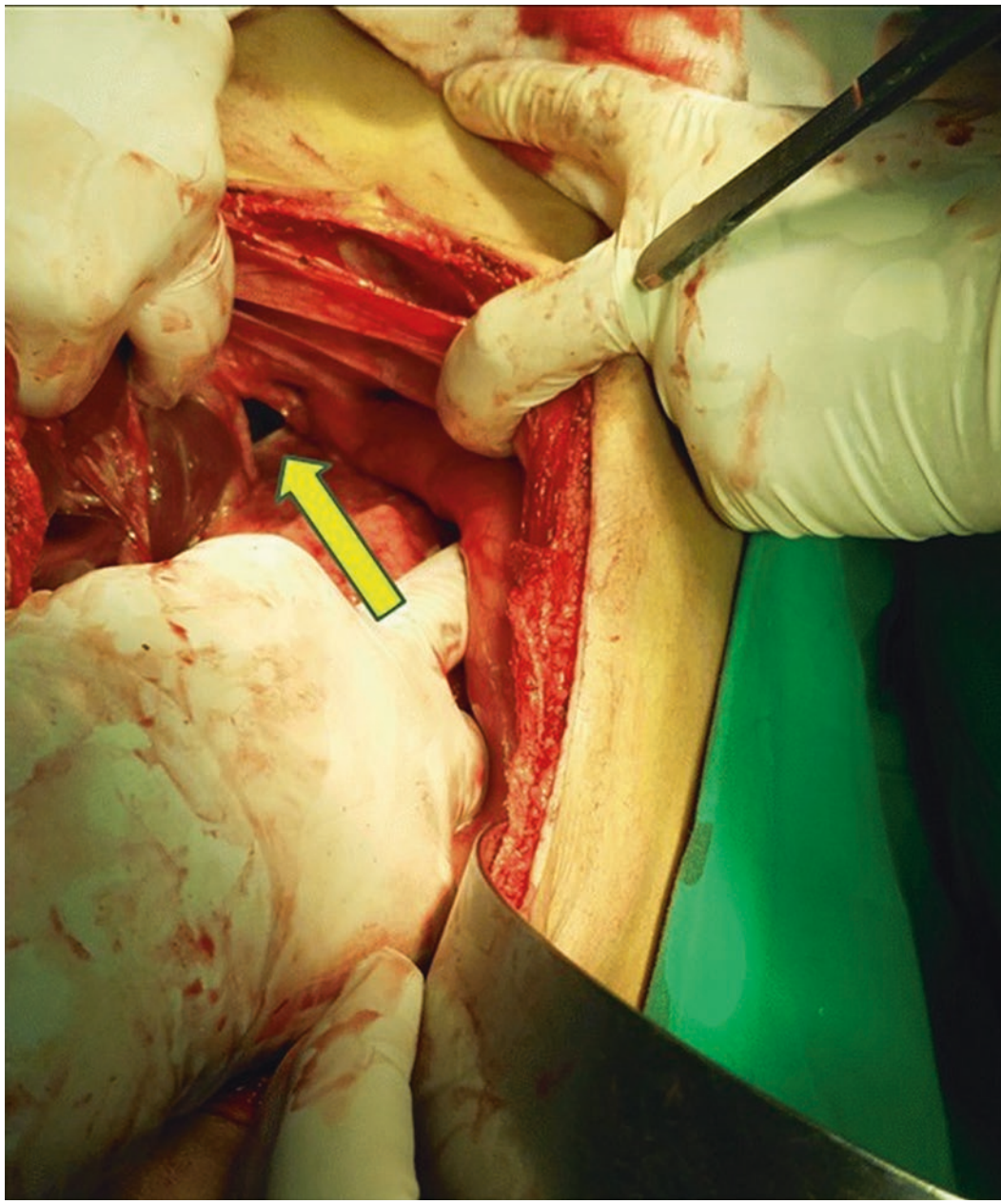

Fig. 9 Intra-operative view of Morgagni's defect (yellow arrow). From Ref. [23]

of recurrence, for which the sac may act as a lead point. On the other hand some authors do not remove the sac, especially in laparoscopic operations, to avoid the apparition of pneumomediastinum or pneumothorax. In the abdominal approach extirpation of hernia sac may be difficult and risky especially in large, old hernias with dense adhesions to the surrounding structures [1, 4, 10].

The way the diaphragmatic defect is closed depends on the size of the defect and the strength of the defect margins. A tension-free closure is required to prevent recurrence). When on the anterior margin of the defect there

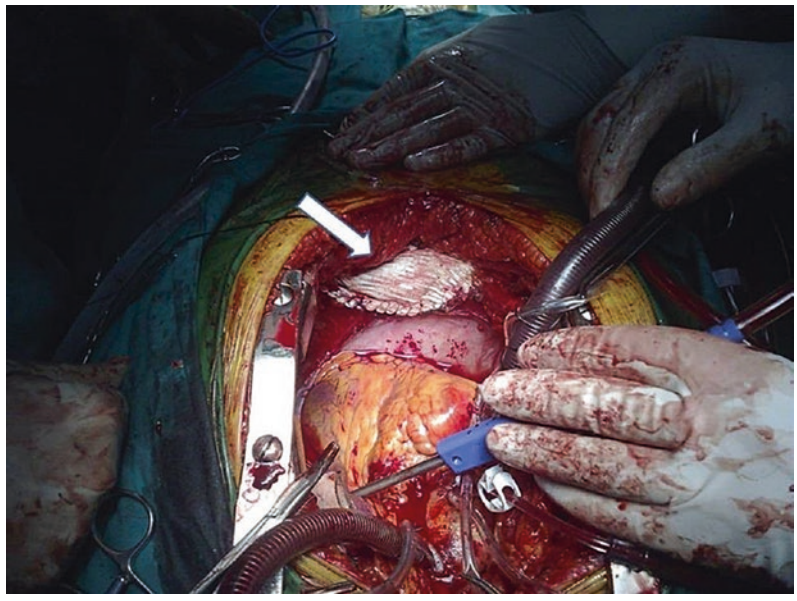

Fig. 10 Final reconstruction of the hernia. A synthetic patch (arrow) was used to close the Morgagni's defect. From Ref. [31]

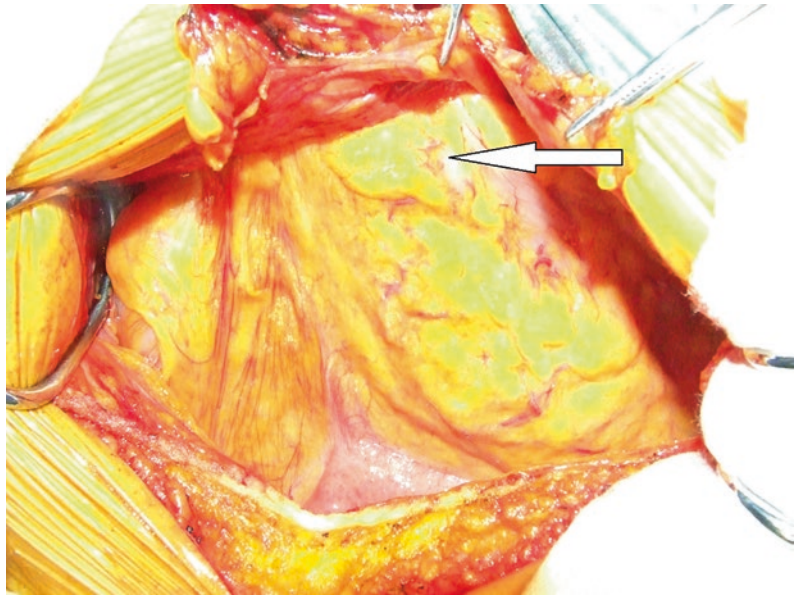

Fig. 11 Morgagni hernia—***abdominal approach***, white arrow shows the herniated viscera

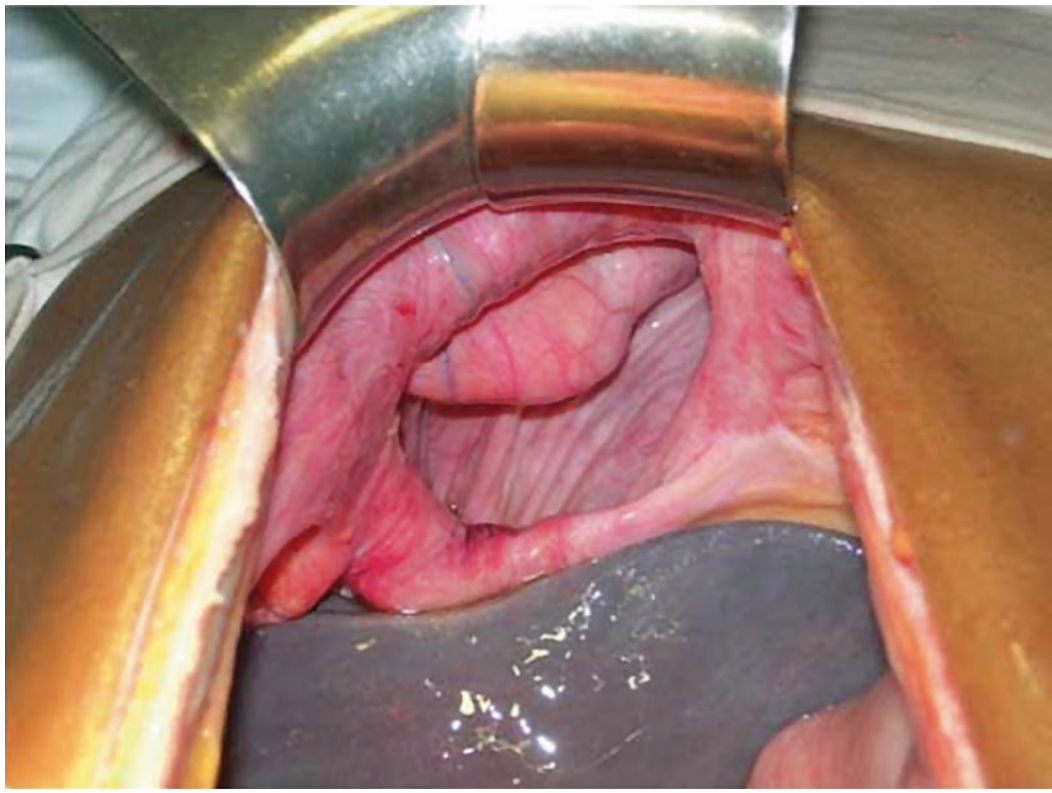

Fig. 12 Intraoperative photo showing the right sided Morgagni's hernial defect. From Ref. [36]

is a rim of diaphragm muscle, it can be closed by primary suture with heavy non-absorbable sutures placed in horizontal mattress fashion.

When anteriorly there is no musculo-fribrous rim, the diaphragm is sutured to the thoracic wall by passing the wires over the proximal rib or through the abdominal wall (Fig. 14) [7, 37, 38]. Non-absorbable sutures are preferred to avoid recurrence [39].

This can be done in small defects, larger defects require repair with prosthetic material [41], to obtain a tension free closure [40, 41]. Dual meshes are recommended to minimize the risks of adhesions to the prosthetic surface [10, 32, 42]. The primary closure can also be reinforced by using a mesh [43].

This can all be achieved by **minimally invasive surgery**. Because of the obvious advantages: reduction in trauma and postoperative pain, lower morbidity, a faster recovery with a shorter hospital stay and positive cosmetic aspect, laparoscopy is considered today the gold standard [24, 38, 44–47]. Kuster G.G.R. reported the first laparoscopic repair of a Morgagni hernia in 1992 [47, 48]. Robotic approaches using the Da Vinci system have also been described [49–51].

The use of meshes is more prevalent in the minimally invasive approach [52]. Some authors use full thickness parietal sutures with extracorporeal knots under the subcutaneous tissue, for a more secure closure of the defect [39]. Single incision ***laparoscopic surgery*** has also been utilised in the treatment of these hernias. The authors describe a single umbilical skin incision through which 3 ports are inserted through separate fascia incisions [53].

In the thoracic approach, after the thoracotomy is made, the sac is identified and entered, the abdominal herniated organs are inspected for damage and then reduced. The sac is dissected (easier through the thorax) and resected. The

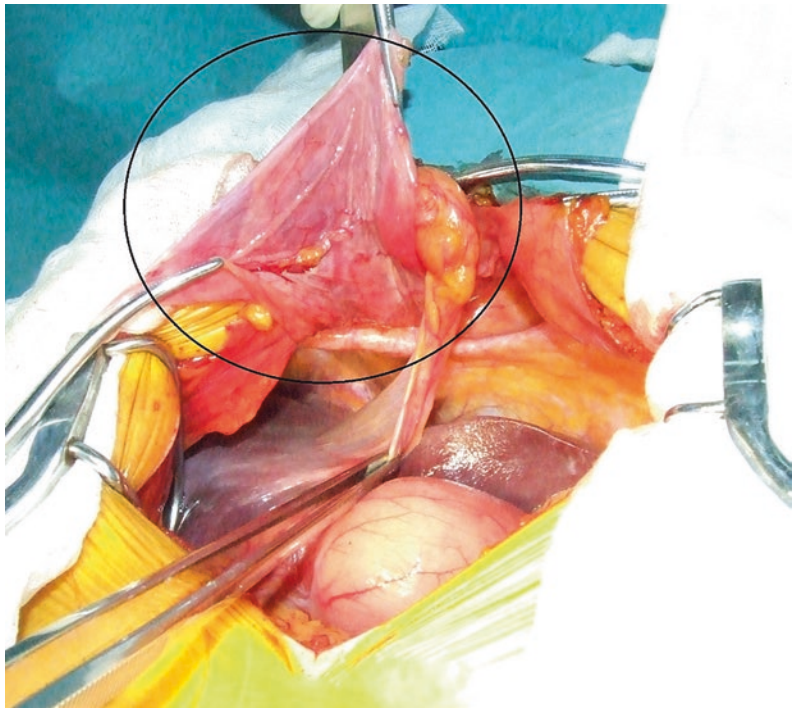

Fig. 13 Morgagni hernia—black circle shows the hernial sac

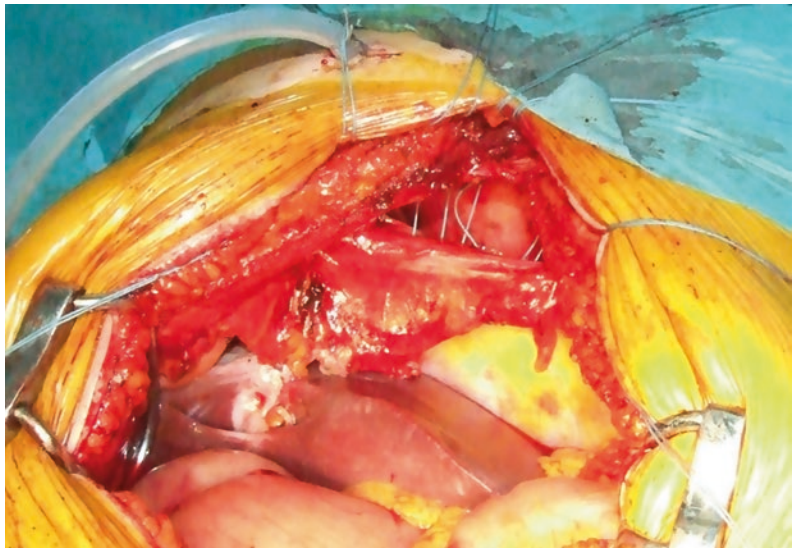

Fig. 14 Morgagni hernia—diaphragmatic defect closure by passing the wires over the proximal rib (white arrows)

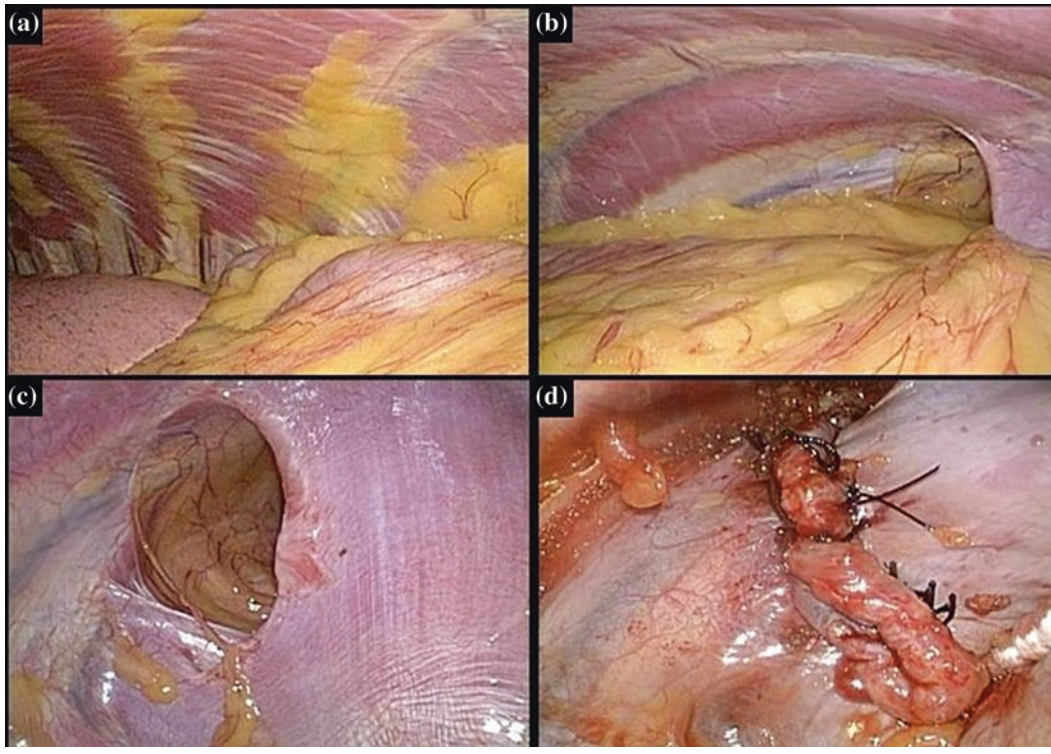

Fig. 15 Surgical findings with thoracoscopy. **a** The left colon and spleen were identified in the left thoracic cavity under thoracoscopy. No hernia sac was found. **b** The left colon and spleen appeared to have herniated through a left posterior diaphragmatic defect, as indicated by the preoperative chest computed tomography. **c** The diaphragmatic defect, 5 cm × 6 cm in size, had a smooth circular edge and showed gradual expansion at the thoracic wall. **d** The defect was closed using a single layer primary closure method with interrupted non-absorbable sutures. From Ref. [55]

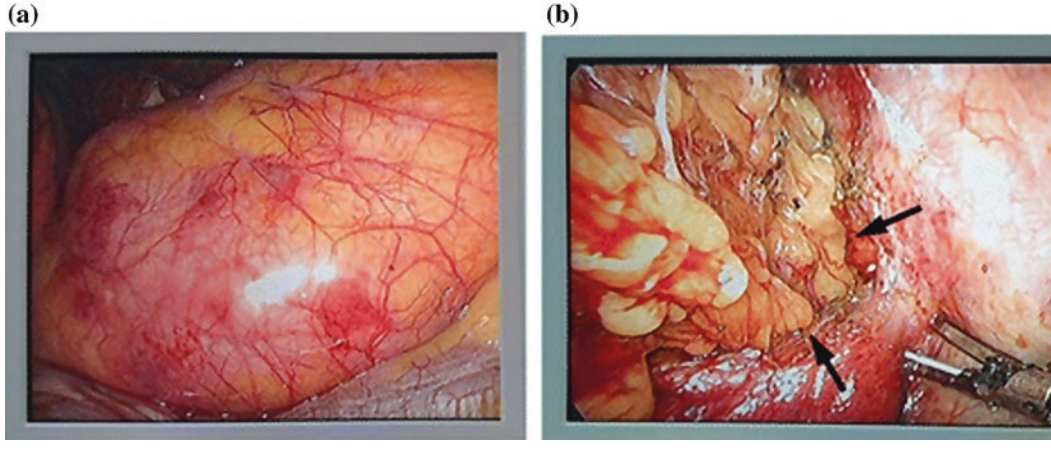

Fig. 16 Thoracoscopic view of the Bochdalek hernia. The retroperitoneal adipose tissue was herniated into the thoracic cavity through the diaphragmatic defect (**a**), and the black arrow indicates the diaphragmatic defect margins (**b**). From Ref. [56]

diaphragmatic defect is closed by suturing its free margin to the thoracic wall with non-absorbable sutures. The pleural space is drained with an intercostal tube connected to an underwater-seal system [7]. Large hernias may necessitate a combined transthoracic and transabdominal approach to permit easier reduction of the abdominal organs from the chest [54].

Thoracoscopic approaches have also been described; the operation follows basically the same steps as in open surgery (Figs. 15 and 16) [55, 56]. Mini-invasive thoracic approaches obviate the risk of pneumothorax or pneumomediastinum which may complicate laparoscopy [34, 55].

The outcome of surgical repair is usually excellent, recurrences are exceptional. Operative morbidity and mortality are low, encountered mostly in patients with complications (gastric volvulus, intestinal occlusion) [4].

Self-study

1. Which statement is/are true:
   a. Morgagni hernia appears mostly on the right side, despite protection from the liver.
   b. The hernias contain only omentum, but the transverse colon, small bowel, stomach or liver may also be implicated.
   c. High-resolution CT is the gold standard in the imaging of Morgagni hernia.
   d. The treatment for retrocostoxiphoid hernia is eminently surgical.
2. Which statements are true:
   a. Surgical repair is indicated even in asymptomatic patients to prevent the onset of life threatening complications such as: hernia incarceration, bowel obstruction, strangulation, or gastric volvulus.
   b. Abdominal approach can be done by a xipho-ombilical incision (the preferred one) or by a subcostal, or paramedian incision.
   c. Thoracic approach is preferred in case of uncertain diagnosis (a mediastinal tumour is suspected).
   d. Morgagni hernia always has a peritoneal sac.

Answers

1. Which statement is/are true:
   a. CORRECT.
   b. CORRECT.
   c. CORRECT.
   d. CORRECT.
2. Which statements are true:
   a. CORRECT.
   b. CORRECT.
   c. CORRECT.
   d. CORRECT.

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Intraoperative Accidents and Postoperative Complications in the Thoracoabdominal Pathology

Adrian Zehnder and Gregor J. Kocher

Key Points

- Complications on the thoracoabdominal border affect both thoracic and abdominal cavity and therefore may hamper a straightforward treatment.
- Parenchymatous organs such as liver and spleen are at risk during diaphragm plication.
- Leakage of the esophagojejunal anastomosis leads to different types of salvage regimens such as stent placement, vacuum therapy, over-the-scope clipping or surgery.
- The treatment of postoperative chylothorax can be achieved equally by conservative or minimally invasive procedures.

General Considerations/Introduction

As discussed in the preceding chapters, treatment of pathologies in the region of the thoracoabdominal border can be quite demanding and are subsequently also associated with an elevated risk for both, major intraoperative events and postoperative complications. Since not only the thoracic, but also the abdominal cavity is involved, each of them can be affected by adverse events.

Recent reports show a relevant influence of intraoperative as well as postoperative complications on readmission rates. For low risk patients after lobectomy for example, readmission rates of up to 11.7% have been reported and therefore such readmissions also are of economic relevance and are furthermore also used as a tool for the assessment of surgical quality. Each comorbidity increases the risk of readmission by approximately 2.0% and each postoperative complication increases this rate by 2.7% [1]. On the other hand, studies which focused on abdominal surgery alone, did show a more than 2-fold increase in 30-day readmissions. Besides intraoperative adverse events, the age and American Society of Anesthesiology classification ≥ 3 are as well predictors of readmission rates [2, 3]. Kaafarani et al. [5] presented a novel grading system for intraoperative adverse events and Rosenthal et al. [6] proposed such a classification similar to the Clavien-Dindo classification for postoperative complications [4–6]. The authors suggest that classification of intraoperative adverse events might help in a number of settings, such as research and development, educational settings/institutional benchmarking, risk management and patient management to anticipate postoperative problems. This has

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already been shown for the classification of postoperative complications [7].

Pathologies on the thoracoabdominal border in general do apply to those involving two defined cavities, each of which has its own risk profile and vulnerability. One can conclude that both together will raise the impact of any incident. Esophagus/stomach and diaphragm are the typical organs where treatment involves the thoracic as well as the abdominal cavity.

Because several parenchymatous and well perfused organs lie in close proximity to the thoracoabdominal border, operations in this region carry a certain risk for intraoperative and postoperative bleeding. The liver and the spleen for example, have a strong relationship with the diaphragm. Therefore, when performing a procedure on the diaphragm, these structures must be carefully identified and protected against unintended injury.

In the following, different aspects of adverse events (intraoperative and postoperative) for specific procedures will be discussed. Since not all of these procedures can be discussed in detail, we focused on the most relevant ones. Furthermore problems such as bronchobiliary fistula and subphrenic abscess have been already discussed in the chapters "Bronchobiliary Fistula" and "Subphrenic Abscess", respectively.

Please be aware that bronchobiliary fistulas may not only occur after major liver resections, but also after interventional procedures such as TACE and radiofrequency ablation [8].

Subphrenic abscesses can occur as a complication after abdominal surgery (lost gallstones, advanced appendicitis, colonic perforation, liver or spleen surgery etc.) but also per continuitatem through the diaphragm from a prolonged pneumonia/empyema. In case of subphrenic abscesses, which are often addressed with sonographic or CT-guided pig-tail drainages, it is not infrequent that the track of punction accidently goes through the thoracic cavity and subsequently the bacterial load can spread into the previously sterile thoracic cavity. This can lead to a complicated effusion and later to an empyema. To avoid such problems, interventional approaches through endoscopic-guided ultrasound (EUS) have been described [9].

The following table (Table 1) gives a general overview of the main postoperative complications in the region of the thoracoabdominal border [10].

Diaphragm

Diaphragmatic plication/resection

Thoracoscopic diaphragmatic plication for diaphragmatic paralysis with consecutive eventration and respiratory compromise is a desirable alternative to standard thoracotomy.

Both scenarios, the open as well as the minimally invasive approach, carry a certain risk of injury of the intraabdominal organs which lie in close proximity to the corresponding part of the diaphragm. In order to avoid or minimize the risk of any inadvertent injury to intraabdominal organs caused by deep stitches, some authors have described techniques using an endostapling device for the resection of the abundant diaphragm. Still, additional oversewing of the staple line is advised, which can certainly be

Table 1 Postoperative complications

Postoperative esophageal leak
Intraoperative perforation/bleeding
Esophagus/stomach
Liver
Spleen
Stenosis (as a late complication)
Respiratory Complications
Pneumonia
Pulmonary embolism
Empyema
Pneumothorax (requiring chest tube)
Chylothorax/chyle leak
Cardiac Complications
Myocardial infarction
Atrial fibrillation
Congestive heart failure
Neurologic Complications
Cerebral vascular accident
Seizure
Port site hernia
Diaphragmatic hernia
Wound seroma (requiring drainage)
Renal failure

done with greater ease after stapling, since the diaphragm is already flattened. This leaves only a small risk for an intraabdominal organ injury. Consequences would be bleeding or hollow organ perforation with the need of an immediate abdominal operative revision and a relevant impact on the patient's perioperative course [11, 12].

In any case of stapling of the diaphragm, whether it is used for diaphragmatic plication or diaphragmatic resection for other purposes, an additional reinforcement of the staple line is strongly recommended. In cases where only stapling was used, postoperative rupture of the staple line with herniation of intraabdominal organs has been described. Such a complication may either occur shortly after surgery, or even after several weeks or months [11, 13]. Symptoms of diaphragmatic rupture are often vague, such as upper abdominal or lower chest pain, sometimes with nausea and vomiting. Diagnosis is usually achieved by computed tomography. For operative correction, the use of a mesh is advocated, which on the left side can mainly be done laparoscopically.

Abdominal procedures

Even if a diaphragmatic hernia following abdominal surgery is quite uncommon, there are some cases described where it develops after deroofing of a liver cyst, for example. Of course, also the "usual" complications such as bile leakage, ascites and pleural effusion can occur. These are primarly abdominal complications [14].

Iatrogenic hernias can also occur after other abdominal procedures such as laparoscopic cholecystectomy, laparoscopic hepatectomy, splenectomy, laparoscopic gastric banding, pancreatectomy, gastrectomy or liver transplantation. These hernias usually present late, as reported in 5–62% of cases in different series. Electrocautery or other energy devices as well as grasping instruments may cause a weak point in the diaphragm, which transforms into a hernia during the following period [14].

Symptoms are mainly chronic such as upper abdominal and lower chest pain, reflux after meals or nausea and dyspnea. But they can also present/develop as acute epigastric pain, vomiting or intestinal obstruction.

Even if it is a good screening tool, only 50% of patients show abnormalities in a plain chest X-ray. Therefore, CT scan is the best imaging modality to diagnose diaphragmatic hernia [15].

Operative approaches for correction include an access through the thoracic as well as the abdominal cavity, while the length of stay is shortest after a laparoscopic procedure. A prosthetic mesh is mainly used on the left side, whereas on the right side, a suture with non-absorbable material might be sufficient [14, 15].

Esophagus/Stomach

Carcinoma

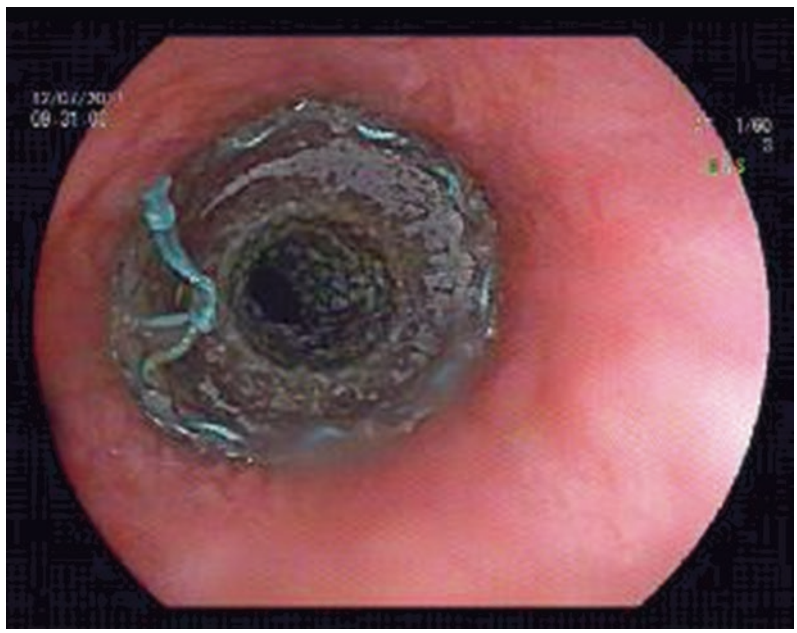
In Western countries the incidence of adenocarcinoma at the esophagogastric junction (AEG) has increased steadily in recent years. Even if these tumors seem to constitute a particular entity from a clinicopathological point of view, management remains controversial [16]. Treatment of choice consists of surgery, but prognosis is still poor. The choice of the procedure is usually based on tumor site on one hand and surgeon preference on the other hand. Both criteria are used in the intent of achieving complete surgical resection.

Irrespective of the reconstruction, wheter it is a mechanical esophagogastric anastomosis after proximal gastrectomy or a Roux-en-Y esophagojejunal anastomosis after total gastrectomy, the anastomosis comes to lie close to the thoracoabdominal border. Therefore, in case of insufficiency, the thoracic and/or the abdominal cavity can be affected. Esophagojejunal anastomotic leakage (EJAL) constitutes one of the most serious and life-threatening complications. Carboni et al. [21] delineates a reported incidence of 2.9–9% for esophagojejunal anastomotic leakage. Others report a rate around 3.5–19% for anastomotic leakage and 0.7–9.6%

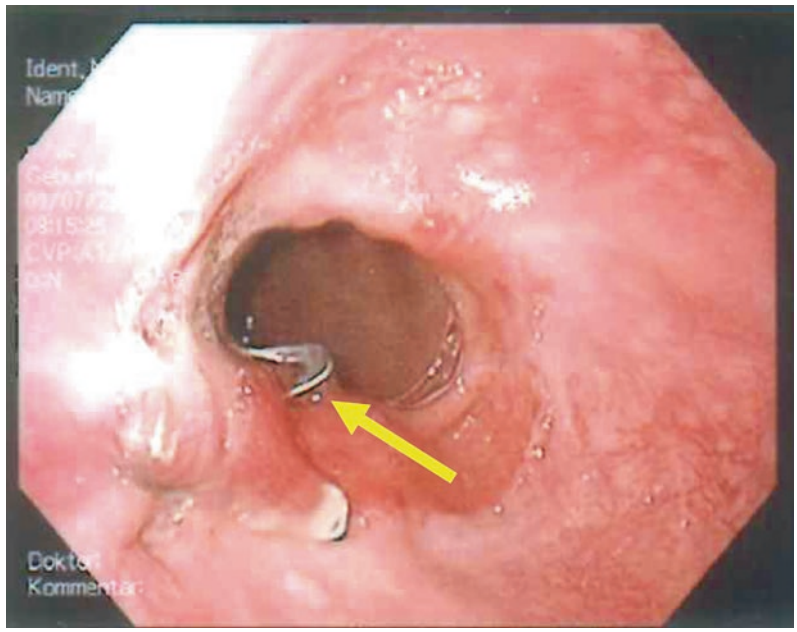
for perioperative mortality as well as a perioperative morbidity of 33–81% in esophageal cancer surgery in general [17, 18]. Cervical anastomosis usually tends to be more prone to insufficiency since the distance for pulling up of the stomach is much longer and blood supply may therefore be limited, even if this difference is less obvious in minimal-invasive procedures [19]. On the other hand, dealing with the circumstances of an anastomotic leakage in the region of the neck are rather simple and therefore should result in a decreased morbidity (e.g. less pulmonary complications; 16% vs. 29%, not significant) and mortality (9% vs. 14%, not significant) rate compared to the leakage of an intrathoracic anastomosis as neither thoracic nor abdominal cavity is involved [20].

Most EJAL treatment consists of conservative management, endoscopic therapy or surgery. Nevertheless, this complication leads to increased mortality rates and prolonged hospital stay, though representing a very challenging event [21].

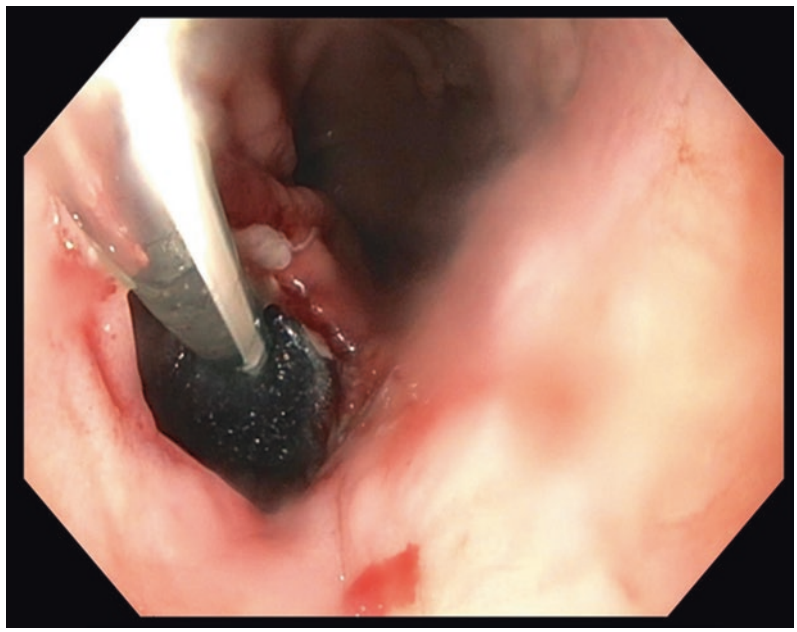
Diagnostic tools consist of CT-scan, contrast studies or endoscopy. If there is still some sort of drain in place this might help in the judgement of potential findings. Preoperative chemotherapy and/or radiotherapy has been found not to be associated with a higher perioperative morbidity and mortality [17]. According to an algorithm proposed by Carboni et al. leakage from a <10% dehiscence can be treated conservatively if the patients state allows such a course of action. In case of 10–50% dehiscence, an endoscopic procedure with stents or over-the-scope-clips (OTSC) must be considered [21] (Pictures 1 and 2). During the last few years, due to technical development of the tools in use, numbers and indications have raised. With stents, technical success rates are reported up to 100% and complete healing rates of the leak are certainly impressive with 81%. Despite an initial successful deployment of the stent, it has to be noted that reported failures of complete healing can also be due to stent migration which is reported to range from 10 to 20%, favoring metal over plastic stents, regardless whether covered or uncovered versions. Outcomes are comparable to a surgical approach and usually 4 weeks should be sufficient time for tissue healing. Additional drainage procedures to control sepsis are often necessary [22]. Beside



Picture 1 Esophageal stent in place with EJAL (provided by B. Magdeburg)



Picture 2 Over-the-scope clip, partly incorporatet (provided by U. Peter)



Picture 3 Endo-SPONGE® in place/dehiscence for EJAL (provided by U. Peter)

stents or clips, negative pressure systems have proven to be very useful, since they can be put in place via endoscopic route, allowing complete healing within 4 weeks or less (Picture 3). One drawback when using an Endo-SPONGE® is the repetitive need for endoscopic interventions [23]. In case of >50% leakage with necrosis at the anastomosis, a surgical revision

is appropriate in most patients, as well as in a deteriorated state with mediastinitis. In these patients, the surgical approach means either primary repair or reconstruction of the anastomosis as well as drainage, total esophagectomy and diversion in case of mediastinitis and clinical signs of shock [17, 21].

While surgery is the sole mainstay of treatment for gastric cancer, there is still some debate about the significance of complications, anastomotic leakage in particular, for long-term survival. There is some evidence that complications might be a major independent factor, since prolonged inflammatory response could promote the metastasis of residual tumor cells due to host immunosuppression. Moreover it is assumed, that extended resection or lymph node dissection can lead to significantly higher postoperative mortality, morbidity, and reoperation rates [24].

Late complications: Stenosis

Benign anastomotic strictures are not uncommon after esophagectomy, especially when using a transhiatal approach. Due to an additional impairement of the often already limited nutritional status, such strictures can have a relevant impact on postoperative recovery and quality of life. Symptomatic anastomotic strictures are defined as dysphagia requiring endoscopic dilatation. The incidence is reported to be up to 63%. The main reasons for anastomotic stricture formation seem to be subclinical ischemia, anastomotic leakage (resulting in more extensive formation of dense scar tissue) or in case of a proximal conduit ischemia, respectively [25].

Usually, endoscopic dilation is considered for patients with dysphagia score grade ≥ 2 (Table 2) and a corresponding finding during gastroscopy. Even stenoses with a diameter of around 11 mm or more can profit from an intervention. In case of diameters of <15 mm, repeated dilation are usually necessary, whereas for diameters of >18 mm only symptomatic patients (dysphagia score ≥ 2) will need repeated dilations [26].

In fact, transhiatal esophagectomy has been classified, among other factors, as an independent risk factor for anastomotic strictures. Transhiatal resection and anastomotic leakage also predict refractory strictures which often require >5 dilations [26]. Circular-stapled anastomosis also seems to be associated with a higher risk for stenosis compared to linear-stapled or hand-sewn anastomosis [26, 27].

Table 2 Dysphagia score

Grade 0	Normal diet
Grade 1	Ability to swallow a semi-solid diet
Grade 2	Ability to swallow a soft diet
Grade 2	Ability to swallow liquids only
Grade 4	Complete dysphagia

Therapeutic strategies not only consist of dilation of the stenosis but also stent-based procedures are described, as well as steroid injections or the use of a needle-knife. Some studies found no prolonged dysphagia-free period comparing dilation with corticoid injection versus dilation alone. This might undermine the widely shared notion that stenosis has only a very little inflammatory component [25]. On the other hand, there is some evidence that Mitomycin C might have a positive impact if combined with the aforementioned procedures. The substance is usually rubbed in every quadrant using a pledged cotton, with an application time of 1–3 minutes per quadrant [28].

Concerning stent-based endoscopic interventions, only about 23–27% of patients experience a long-lasting treatment success, defined as durable relief of symptoms after stent removal. Anchoring of the stent in order to prevent stent migration is the main concern here. There are some antimigration features of the self-expandable metal stents, which can help to keep the device in place. The stent flares should have an increased diameter as well as no covering in order to fix the stent by some degree of localized tissue ingrowth. Besides that, fully covered stents are thought to have a low late complication in addition to the feature of easy removal [29]. Addition of struts to the outer stent covering and specialized shapes can be an additional factor to minimize migration. Even though,

stents migrate frequently despite these design modifications [25].

In patients receiving esophageal stents the adverse event rate is 30–35% and this rate even increases with a longer stent indwelling time. The most common long-term adverse events present in recurrent dysphagia and fistula formation, while stent-related esophageal perforation is rare. Patients may suffer from retrosternal pain after stent placement in up to 60% of cases. In this case nonsteroidal anti-inflammatory drugs may be used to reduce discomfort [25]. Concerning the optimal treatment duration when using a stent, there is no clear consensus, but most authors recommend endoscopic stent removal after 4 to 6 weeks if no migration occurs [29]. Stent migration can cause mechanical ileus, especially if the device gets stuck in the small-bowel or a perforation is imminent. In this case urgent surgical stent removal has to be undertaken which drastically increases morbidity in these patients [30].

Achalasia and epiphrenic diverticula

In most cases of epiphrenic diverticula (75–100% of patients) an underlying motility disorder such as achalasia or nutcracker esophagus results in the formation of the diverticulum and therefore it is vital that the treatment addresses both findings together in symptomatic patients [10].

For the treatment of achalasia usually a myotomy in combination with a fundoplication is indicated, whereas it has to be noted that this kind of procedure is associated with a significant risk for postoperative reflux disease (48% without fundoplication vs. 9.5% with Dor or Toupet fundoplication). The preferred approach is therefore laparoscopy with transection of the diverticulum by means of an endostapler and an additional fundoplication. For resection of the diverticulum, most surgeons prefer to use an endostapler with oversewing of the staple-line, since leakage of the resection line is the main postoperative concern with reported leakage rates ranging from 0 to 33% with a general morbidity rate up to 75%. Empyema, abscess and sepsis are the most severe consequences following leakage. They occur in 5.3–37.5% of cases. Since oversewing of the staple line results in less complications this technique is advocated whenever possible. As for other locations in the gastrointestinal tract, the number of staple cartridges used shows an elevated risk for leakage, too [31, 32]. Regardless of the surgical technique, mortality rates after the treatment of an epiphrenic diverticulum including the underlying disease range from 0 to 10% [10, 33]. Since the entity is very rare, these numbers vary relevantly depending on the literature. Therapy of major leakage may consist of vacuum-therapy, placement of an esophageal stent or moreover a thoracotomy/laparotomy to operatively address the lesion.

Fundoplication

In anti-reflux surgery there are several techniques described, such as Nissen, Toupet or Dor, with the goal to prevent acid from flowing back in the esophagus, causing discomfort and pain and maybe leading to a Barrett's esophagus which is thought to be an adaptation to chronic acid exposure from reflux esophagitis. These procedures usually can be done in a straightforward manor with a minimally invasive technique and a low complication rate [34].

A common problem with this type of surgery is the gas-bloat syndrome, which causes distent of the stomach due to a reduced ability of belching with a tight closure of the lower esophageal sphincter. The problem, if unsolved and not tolerated by the patient, can occasionally call for a reversion of the initial fundoplication. The incidence of a gas-bloat syndrome ranges from 1 up to 85% [35].

Another feared complication after fundoplication is the formation of a diaphragmatic hernia, especially after Nissen procedure, which can even lead to life-threatening situations when strangulation or perforation occurs, or even cardiovascular and respiratory insufficiency when diagnosis is delayed. Such a herniation can develop rapidly, but more often develops over time. Symptoms are often unspecific and present

in the form of upper abdominal and lower chest pain, nausea, dyspnea, and reflux, which then develop into acute obstructive symptoms, such as severe epigastric pain and vomiting.

Frequently, diagnosis of an iatrogenic diaphragmatic hernia is late after the beginning of symptoms. Nevertheless, surgery is indicated at the time of diagnosis because rapid deterioration can occur in case of strangulation. A CT scan is the preferred diagnostic tool in this situation, followed by endoscopy if the situation is still unclear [36].

As the stomach has a rich blood supply and an extensive submucosal vascular network, gastric necrosis is a rare condition. The above-mentioned gas-bloat syndrome is a well known complication after fundoplication. Sometimes it can cause severe gastric dilatation, but ischemic compromise of the organ is very rare [35, 37].

To ensure a one-way valve effect that prevents gastric reflux, during Nissen or other antireflux procedures, a gastric wrap of the distal esophagus should be performed in order to ensure an adequate compression. When anterograde propulsion is also blocked, distension blocks the periesophageal wrap progressively, thus intragastric pressure will increase and subsequently compromise the organs blood supply. Some studies have shown that an intragastric pressure greater than 20–30 cm H_2O is necessary to compromise its blood supply. Such a situation can be aggravated by other factors, such as gastric outlet obstruction or delayed gastric emptying, which is rather common in patients undergoing antireflux-surgery. With the rising intraluminal pressure, first the venous return is compromised, followed by a restriction of the arterial blood flow, finally leading to ischaemia [35].

Abdominal pain, distension and/or tympanic percussion are typical symptoms but not specific for this problem. Therefore, a high degree of suspicion is needed for early diagnosis of gastric ischemia. A previous history of fundoplication in combination with the aforementioned symptoms should ring the alarm bells and lead to a further diagnostic work-up with plain X-ray and an endoscopic examination.

Chylothorax

An injury of lymphatic vessels, mostly the thoracic duct, resulting in chylothorax can occur after a variety of procedures in the region of the thoracoabdominal border. The most common causes are esophageal resections or mediastinal lymphnode resection in general (e.g. during oncologic lung resections) with an incidence of about 1–3% [38]. Because the chyle contains not only lipids and proteins, but is also filled with lymphocytes, vitamins, immunoglobulins and electrolytes, losing these important components may worsen the patients's postoperative nutritional condition. This can lead to hypovolemia, acidosis, hypoproteinemia and hypocalcemia [39]. Chylothorax as a postoperative complication is also associated with a compromised cardiorespiratory function, as well as a shorter median survival time. Without treatment, mortality rates can get as high as 50% [40]. Means to prevent or minimize the risk for postoperative chylothorax are for example the use of electrocautery or ultrasonic scalpel for the lympadenectomy, or—as routinely performed by some surgeons during esophagectomy—the preemptive identification and ligation of the thoracic duct [33, 41].

Postoperatively chylothorax is easily diagnosed when a chest tube is in place. The typical creamy color is the first and most obvious sign of chylothorax, which can be confirmed by determining triglyceride levels and lymphocytes in the exudate and the serum. During fasting time butter or cream must be administered through the nasogastric tube or jejunostomy to reveal the typical situation. If no drain is in place suspicion must be aroused when major fluids in chest X-ray are found while experiencing newly developed dyspnea [38]. Of course a leakage of any hollow organ must be ruled out. In specialized centers, lymphangiography is considered the gold standard for investigating chylothorax. However, the intervention requires a high level of experience since there are threats of complications such as fat embolism, tissue necrosis or hypersensitivity reaction from contrast material [39]. Nevertheless, in experienced hands,

lymphangiography can not only serve as a diagnostic tool, but in addition serve as a treatment option, offering the possibility of lymphatic duct embolization with high success rates [42].

Primary therapy usually consists of drainage (chest tube), no food with parenteral nutrition for 5–10 days and occasionally the use of subcutaneous somatostatin injections. Also medium-chain triglyceride diet can be administered [33]. If unsuccessful, minimally invasive techniques provide excellent results and low morbidity in case a lymphangiographic intervention is not available. Traditionally, the main indication for lymphangiographic or surgical intervention has been failure of conservative management. Early intervention in patients with high-output fistula might be appropriate in case of leakage rates above 1000 mL/24 h [38].

Summary

Complications on the thoracoabdominal border pose an impact on both the thoracic and abdominal cavity. Therefore, treatment can be quite demanding and consequences for patients are relevant, sometimes even life-threatening. This will also have an implication on the outcome for cancer-specific survival if the underlying disease is so.

Pathologies of the diaphragm can be addressed from above (intrathoracic) or below (intraabominal). Since the liver and the spleen lie close to it and are well perfused organs, they are in some danger for intra- and postoperative bleeding complications. Another issue is a diaphragmatic hernia that can lead to an incarceration of the intestine. Hernias are usually closed with placement of a prosthetic mesh.

Adenocarcinoma at the esophagogastric junction (AEG) has increased in recent years. Resection will lead to an anastomosis that lies close to the thoracoabdominal border. The biggest concern is on the insufficiency of this anastomosis and conservative treatment options range from stents to Endo-SPONGE® application. No superiority could be proven yet. Surgical revision is the last option for salvage. Late complication is seen as stenosis which must be followed by repetitive dilation and/or stent placement.

Epiphrenic diverticulum evolves mainly from an underlying disease such as achalasia and should include a simultaneous treatment of both entities. There goes also a certain risk for leakage of the resection line. Treatment follows the principles of esophagojejunal anastomotic leakage.

With fundoplication as anti-reflux surgery we find very rare complications beside the well-known gas-bloat syndrome. Beside a diaphragmatic hernia after Nissen fundoplication there is also severe gastric dilation with ischemic compromise a possible threat.

In both thoracic and abdominal procedures injury of lymphatic vessels, namely the thoracic duct, may occur. Without treatment, mortality rates can get as high as 50%. Conservative, interventional and operative treatment can be administered with similar success rates.

Questions

1. Which strategy is the optimal treatment option for the treatment of a benign stenosis after esophagectomy?
   a. Immediate operative revision and re-do of the anastomosis.
   b. Placing a stent for 4–6 weeks.
   c. Repeated endoscopic dilation with or without stent-placement.
   d. Mitomycin C applications.
2. Which of the following statements in case of a chylothorax is true?
   a. Chest tube placement and fasting with parenteral nutrition for 2–3 days.
   b. Quality of exudate—creamy color—, determining triglyceride levels and lymphocytes in the exudate and the serum are the only way to get evidence of a chylothorax.
   c. (A) and (B) is correct.
   d. Neither (A) nor (B) is correct.

Answers

1. Which strategy is the optimal treatment option for the treatment of a benign stenosis after esophagectomy?
   a. A surgical re-intervention should be considered last, since the etiology of the stenosis is benign.
   b. Stent treatment alone may be hampered by several issues such as displacement or migration.
   c. Correct answer. Benign strictures should be subject to repeated endoscopic dilations (diameter < 15 mm or in symptomatic patients). Additionally patients may benefit from a temporary stent placement.
   d. Mitomycin C is only useful as an adjunct.
2. Which one of the following statements in case of a chylothorax is true?
   a. Chest tube placement and fasting with parenteral nutrition is mandatory as first-line therapy, but at least 5 (up to 10) days are recommended to allow lymphatic vessels to seal.
   b. A gold standard in diagnostics for determine leakage of lymphatic structures, especially thoracic duct, is lymphangiography. In specialized centers it should be considered as a standard diagnostic.
   c. Wrong.
   d. Correct answer.

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Anterior/Posterior Thoracoabdominal Approaches

Sabit Sarikaya, Emre Selçuk, and Kaan Kırali

Key Points

- The thoracoabdominal incision providse a surgical exposure of the thorax and abdominal cavities simultaneously
- The thoracoabdominal incision is used in re-operative anti-reflux surgery
- esophageal malignancies
- thoracoabdominal aortic surgery and resection of retroperitoneal large tumors
- The main steps of thoracoabdominal incision are thoracotomy
- diaphragm incision and laparotomy
- It is essential to determine the correct incision line and patient position depending on the indication.

Introduction

The thoracoabdominal surgical approach means the exploration of the thorax and abdominal cavities simultaneously via a single or staged incision. This approach provides excellent surgical exposure for wide dissections in various indications. The surgeon can access the lung, esophagus, stomach, diaphragm, liver, inferior vena cava, kidney, adrenal gland, and also thoracoabdominal aorta thanks to the modifications of the thoracoabdominal incision.

History

Thoracoabdominal approach was first used by Lannelongue at the end of the 19th century in order to expose upper left cadran of the abdomen [1]. The first thoracoabdominal incision, similar to the current technique, was performed by Janeway and Green in 1910 [2]. In this study, a tumor invading distal esophagus and gastric cardia was resected with a two-stage surgical technique consisting of thoracotomy and then laparotomy. Seo and Oshawa performed the first successful single staged thoracoabdominal incision series for esophagogastrectomy in 1933 [3]. He extended the median or paramedian abdominal incision to 7th intercostal space in this technique [2]. In case of tumors of lower esophagus, Garlock recommended the exploration of

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intra-abdominal part of the esophagus for assessment of resectability of a tumor as the first step [4]. In 1947, Carter recommended thoracoabdominal incision to perform splenectomy in case of extensive splenomegaly [5]. The first report of full resection of large, fusiform descending aortic aneurysm via left thoracoabdominal incision was published by De Bakey [6]. In 1977, Omnger underlined that thoracoabdominal approach was useful not only for carcinomas of the esophagus but also in the surgical management of benign pathologies of the esophagus [7].

Indications

The thoracoabdominal approach is a logical option in many pathologies requiring thoracic cavity, retroperitoneal and upper abdominal exploration. First, this technique is indicated for the resection of carsinomas located in esophagogastric junction, the lower third part of the esophagus carcinomas, and also resection of the middle-third esophageal carcinomas in selected cases. Thanks to the extension of the abdominal portion of the incision to the caudal; total gastrectomy and Roux-en-Y reconstruction of the esophagus can be performed [8, 9]. Of note, aorta limits the direct surgical vision of the esophagus when the tumor is located above the carina.

Currently, minimally invasive approaches (laparoscopy and thoracoscopy) for re-operative antireflux surgery are quite common [11]. Nevertheless, some patients require open surgery because of massive adhesions [12]. This technique provides excellent exposure for complex esophageal reconstuction thanks to allowing retraction of the costal cage. Moreover, in selected cases, the thoracoabdominal approach is still a valid option for other benign esophagus diseases. (esophageal stricture, primary motility disorder, paraesophageal hernia, etc..) [13].

Although this procedure was first described for gatrointestinal surgery; the similar technique is used by different surgical specialists for the treatment of various diseases. Vascular surgeons use this approach for reconstruction of the thoracoabdominal aorta in the aneurysmal or occlusive diseases of the aorta. According to the level of aortic pathology, a single left thoracoabdominal incision (straight or oblique) or two separate incisions with costal margin-sparing technique can be preferred [14–16].

Management of thoracoabdominal trauma is one of the most challenging injuries due to diagnostic dilemma between two major cavities. Additionally diaphragma laseration may reduce predictive value of abdominal examination. On the other hand laseration of diaphragma may mask possible thoracic hemoragies despite the chest tube. If unexplained hemodynamic instability persists; preferring thoracoabdominal incision as a first step may be a logical option for damage control surgery [17, 18].

When extrathoracic approaches do not provide optimal surgical exposure for complete resection of the tumorous area and adequate vascular control, the left or right thoracoabdominal incision provides an excellent direct surgical vision for large retroperitoneal tumors [19, 20]. In case of urological tumors invading inferior vena cava (especially if a tumor thrombus extending to the intrahepatic veins is present); a single right thoracoabdominal incision provides direct surgical vision to connect cardiopulmonary bypass and also to perform radical nephrectomy or adrenalectomy [21]. The thoracoabdominal approach might be useful for right-sided hepatic resection in selected cases requiring additional hepatic mobilization [22]. Finally, this approach is applied in thoracic scoliosis operations. In this procedure, an abdominal incision is performed retroperitoneally for the lumbar portion of the deformity [23, 24].

Anesthesia Management

Right radial artery is preferred for arterial monitoring. Central venous catheter and large peripheral intravenous catheter are inserted. After induction of general anesthesia, the patient is intubated with a left-sided double-lumen endotracheal tube. Alternatively, left bronchial blocker may be used to deflate the left lung during the operation. If a left neck incision is planned for total esophagectomy, no catheterization should be performed on the left arm and left neck. A nasogastric tube should be placed for gastric decompression. Fluid shift secondary to the opening of the two major cavities should be replaced

aggressively during the operation period. The spinal cord and visseral protection principles should be applied to prevent cross-clamp induced ischemia in thoracoabdominal aortic aneurysm operations. Not only wide incision but also costal margin related pain may result in pulmonary complications. Preoperative placement of a thoracic epidural catheter is critical to minimize postoperative incisional pain. The epidural catheter can remain up to 5 days [10]. The patient should be reintubated with a single lumen tube before transport to the intensive care unit.

Operative Techniques

Since the thoracoabdominal approach has been described for the first time, it has undergone many changes in patient positioning, anesthesia management, and incision techniques. Nowadays, various types of thoracoabdominal incision are applied, depending on the localization and pathologies. On the other hand, slightly different incision techniques have been described for similar pathologies. In this section, the operation steps of the standard single-stage left thoracoabdominal incision were emphasized to guide the thoracic surgeons in their surgical applications, avoiding disease-specific details.

Patient Positioning

The essential initial step of the thoracoabdominal approach is appropriate positioning in order to gain excellent surgical exposure. For the left thoracoabdominal approach, the patient's standard position is the right lateral decubitus position (Fig. 1). The patient put in the position of optimal right lateral decubitus for this incision looks similar to corkscrew which is the thoracoabdominal border is evident. In thoracoabdominal aortic surgery, the chest is positioned perpendicularly to the operation table and the abdomen forms an angle of 45 degrees with the operating table [25, 26]. On the other hand, in esophageal operations, the upper torso should be rotated 45 degrees to the left and the abdomen should remain in the nearly supine position so that the distal esophagus can be visible [27].

The left arm is placed on an arm board so that the left arm is almost parallel to the area of the anesthesia. Alternatively, the left arm may be placed on the right arm by placing a support between the two arms. During arm positioning, it is important to adequately support the arm and shoulder to prevent brachial plexus injuries. Intra-venous fluid bags or polymer gel packs should be placed under the right axillary region to elevate the hemithorax and keep immobilized. If cervical esophageal dissection is required, the left shoulder and arm should be previously wrapped with sterile drape. In this way, the left arm can be manipulated sterilely and the neck and thorax incisions can be performed respectively. Hyperextension of the patient in the horizontal plane contributes to surgical exposure by increasing the intercostal distance. The legs are separated with a pillow.

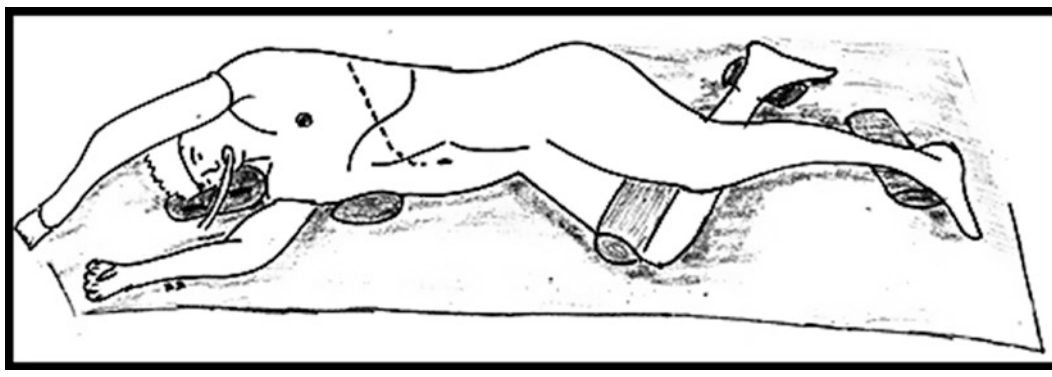

Fig. 1 Right lateral decubitus position for thoracoabdominal incision

Thoracotomy Techniques

The thoracoabdominal incision can be performed as cranio-caudal or caudo-cranial. The incision usually begins with thoracotomy in benign esophageal diseases and aortic procedures. If the distal esophagus tumor is present, the surgeon may initially prefer the exploration of the abdominal component to assess resectability.

The thoracic part of the standard thoracoabdominal incision starts under 2 fingers of the left scapular tip and then continues through the intercostal distance obliquely towards the anteromedial portion. The suitable intercostal space for thoracotomy is determined according to the specific disease. Seventh or eighth intercostal space is preferred for gastroesophageal malignancy, diaphragmatic operations and also aortic pathologies. Thoracotomy should be performed in the 5th or 6th intercostal space for resection of high esophageal tumors [1]. The skin incision is made obliquely towards to the midline of the abdomen along the upper border of the rib. The end of the incision is carried down slightly below the xiphoid process. The subcutaneous tissue and intercostal muscles are divided with electrocautery. It should be noted that the intercostal arteries, veins, and nerves are placed in the lower border of the rib. Serratus anterior and latissimus dorsi muscles can be divided if you need an additional posterosuperior thorax exposure. The incision is carried down through the intercostal space and then the pleural space is opened. Left lung should be deflated at this moment. The left hemithorax should be investigated first after the retractor has been inserted. The left inferior pulmonary ligament is transected in order to superior retraction of the lung. Careful dissection is performed on the inferior mediastinum and thoracoabdominal border, then essential anatomical structures are revealed clearly.

The first seven ribs are directly attached to the sternum. Conversely, 7th to 10th ribs share a common cartilaginous connection to the sternum at costal margin. The costal margin is the inferior edge of the thorax. Costal margin is divided after a thoracotomy. Musculophrenic artery, which is the terminal branch of the left internal mammary artery, should be ligated and divided carefully at this point (Fig. 2).

Diaphragm Incision

The diaphragm is a musculotendinous C-shape structure that separates thorax and abdominal

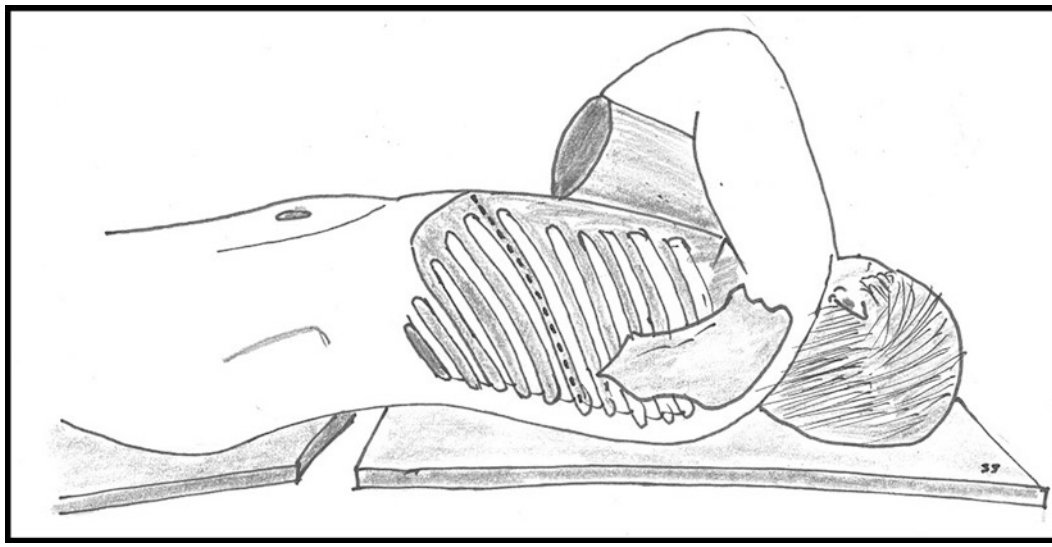

Fig. 2 The thoracotomy incision starts under 2 fingers of the left scapular tip

cavity. The diaphragm should be divided to connect the abdominal and thoracic cavities. It is important to understand the essential anatomy of diaphragm in order to perform complication-free incision. The left phrenic nerve carries down onto the diaphragm through the left pericardial border and then it gives their diaphragmatic branches. Pericardiacophrenic artery and its branches accompany the phrenic nerve through the thoracic side of diaphragm. The main body of phrenic nerve should be identified and preserved during diaphragm incision as much as possible. Generally, it is not possible to inspect phrenic nerve branches due to the small size and also the intramuscular location of nerves in diaphragmatic surface. Also, phrenic vessels (in particular inferior phrenic arteries and branches of pericardiophrenic artery) should be preserved or securely ligated [28].

The diaphragm may be divided in two different techniques according to the indications: radially or circumferentially (Fig. 3).

a. Circumferential incision: This commonly used technique provides excellent visibility of the thoracoabdominal border. The circumferential incision is started from anterior and it continues circumferentially at the periphery of the diaphragm. Diaphragmatic rim should be maintained at least 2–3 cm from the costal arch. The incision can be extended posteriorly as needed especially in esophageal malignancies.If the retroperitoneal approach is planned for thoracoabdominal aorta, the incision should be extended posterolaterally towards the aortic hiatus [29].
b. Radial incision: In this technique, the incision carries out from the diaphragm dome to the esophageal hiatus, after the costal margin is divided. Currently, the radial incision is not popular due to the high risk of phrenic nerve injury and also insufficient surgical exposure. The radial diaphragmatic incision is used when the transperitoneal approach is performed in thoracoabdominal aortic pathologies.

The diaphragm should be retracted with the help of sequential U stitches placed near the incision line. Additionally, these stitches function

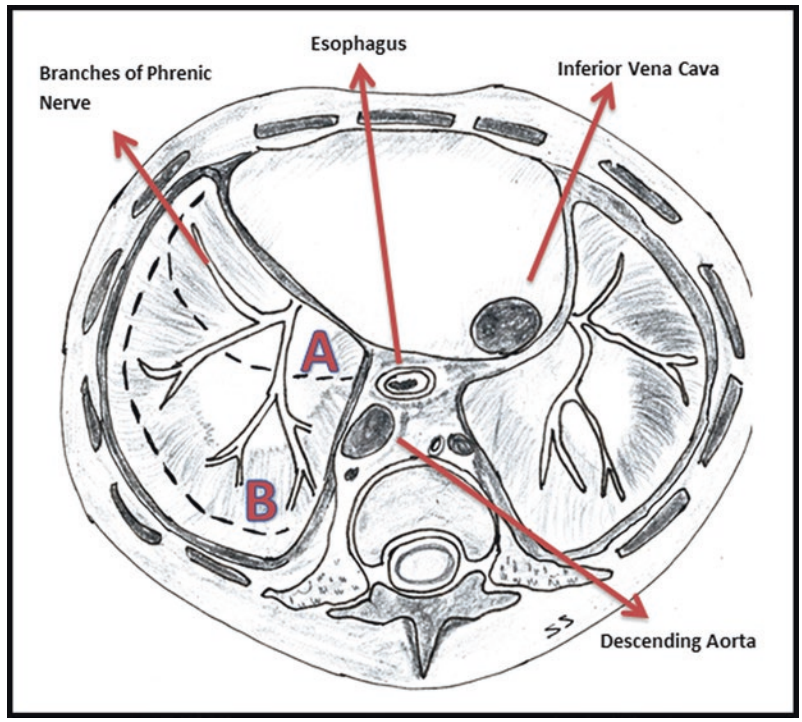

Fig. 3 **a** Radial incision. **b** Circumferential incision

as markers when closing of the diaphragmatic incision. The incisions length can be variable depending on how much exposure is required. It is important to note that the limited incisions of diaphragm improve pulmonary outcomes [30].

Laparotomy Techniques

The median or paramedian abdominal incision can be made for transperitoneal approach. The midline incision commonly preferred due to easy to perform and provide excellent exposure of abdomen and also retroperitoneum [26]. This vertical incision starts from the inferior curvature of the thoracic incision and then passes through the skin, subcutaneous fat, avascular linea alba and peritoneum. The incision usually terminates in the distance between the xiphoid-umbilicus for thoracoabdominal borderline pathologies such as the distal esophagus, proximal stomach, diaphragm, and spleen (Fig. 4). The esophagogastric junction and stomach are easily accessible thanks to upward retraction of the diaphragm. If colonic interposition is required for colonic mobilization, the incision is extended to caudal. Likewise, the incision may be extended to the pubis to reach the distal part of an aneurysm when aortic aneurysm repair is performed.

In the retroperitoneal approach, the peritoneal cavity remains intact. This aproach commonly used for thoracoabdominal aortic pathologies. Transversus abdominis muscle is divided after a paramedian flank incision. Once the retroperitoneal space is entered, visceral organs and peritoneal fascia are mobilized to medially via blunt dissection. The left renal artery must be carefully preserved along the incision line. In the retroperitoneal approach, the fluid shift is

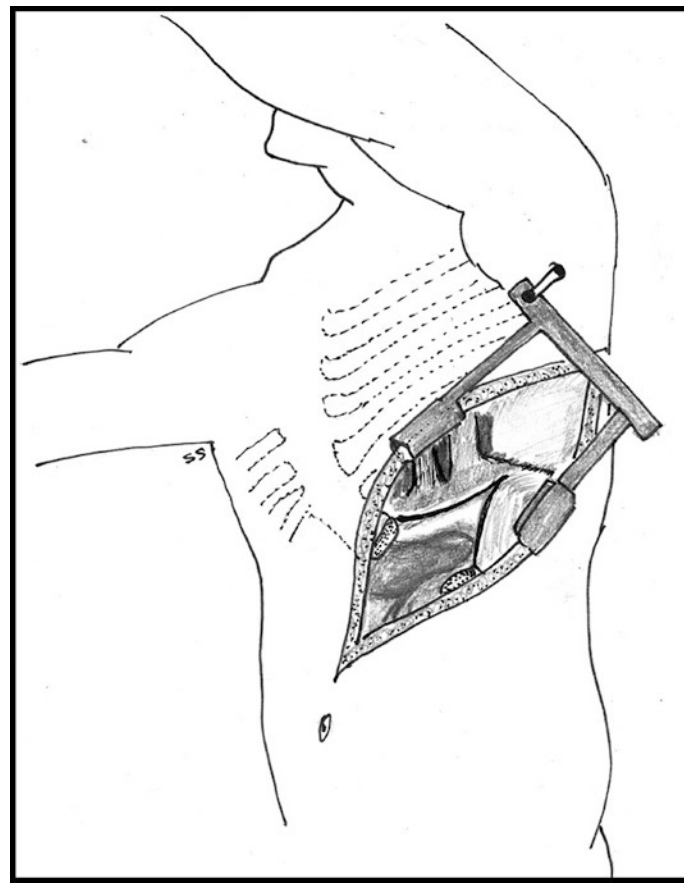

Fig. 4 Left thoracoabdominal approach

fewer than the transperitoneal approach thanks to the fact that peritoneal space is not opened. However, the exposure of the right iliac artery is limited compared to the transperitoneal approach.

Wound Closure

After the completion of surgical procedures and adequate bleeding control, the wound closure step is begins (Fig. 5). The diaphragm is reapproximated before the closure of cavities. Diaphragm closure sutures must be robust and non-absorbable. We routinely use 0-polypropylene sutures for closure diaphragm. The T-shaped incision had been created in the diaphragm by cutting the abdominal oblique and rectus abdominis muscles. The transverse part of T shaped incision represent diaphragmatic incision, the vertical part is made by incision of the abdominal muscles [1]. The previously placed marker stitches are tied and the diaphragm rims are approximated. Figure-of-eight sutures are placed in the attachment point of transverse and vertical incisions, and then tied immediately but not cut instantly. It is used as a second continuous layer to support the previous horizontal sutures. A 28–30 Fr chest tube is inserted. The ribs are approximated with the pericostal figure of eight sutures (No. 1 Vicryl). The abdominal part of the incision is closed in two continuous layers (No. 1 polypropylene). The costal margin is tightly approximated with single 0-polypropylene figure-of-eight suture. The edges of costal margin should be trimmed in

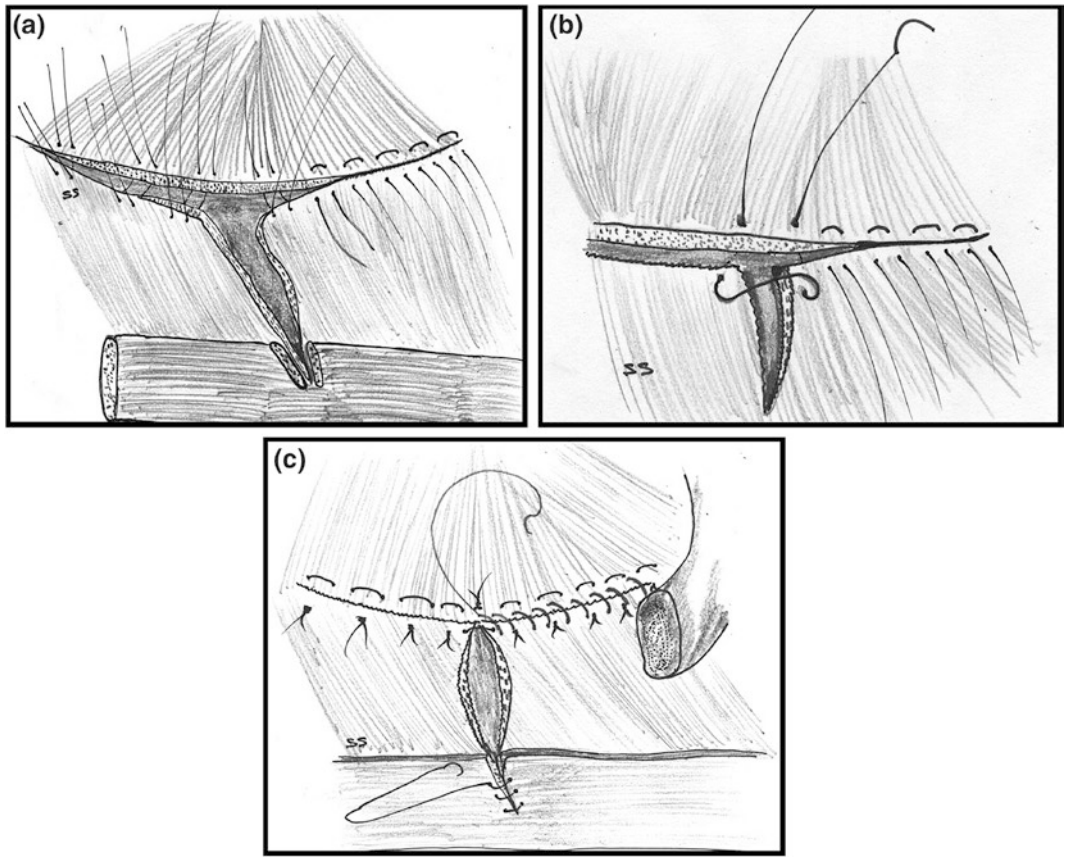

Fig. 5 **a** Firstly, marker stitches should be tied. **b** Figure-of-eight sutures are placed in the attachment point of transverse and vertical incisions. **c** Second continuous layer of diaphragma sutures and closure of rectus sheath

order to prevent possible cartilage detachment. The superficial fascias and subcutaneous layers are closed respectively. Finally, the skin is closed with staples.

Modifications

If thoracic exposure is still insufficient despite the posterior extension, an additional high-level thoracotomy (4th or 5th intercostal space) may be required to perform high intrathoracic esophageal procedures [31]. One or more ribs may be resected to improve the thoracic exposure [32]. In high esophageal procedures, it is important to be alert about intercostal vessels and recurrent laryngeal nerve which can be damaged during mobilization of aortic arc.

In the juxtarenal aortic stenosis, a thoracobifemoral bypass is a logical option in order to avoid secondary atheroma embolism secondary to cross-clamp in the atherosclerotic level. Two separate incisions are required in this technique: anterolateral thoracotomy and reverse J-like abdominal incision (start from 5 cm below of arcus costalis to inguinal area). The advantage is that costal margin remains intact [15]. An alternative technique for the thoracoabdominal aortic aneurysm is the straight incision with rib-cross thoracotomy from axilla to left lumbrical area. This technique facilitates manipulation of the arcus aorta, proximal descending aorta and also abdominal components in one single view [15].

Complications

Because the thoracoabdominal approach requires wide surgical dissection, the surgeon must be alert to the pitfalls at every step. Two types of complications can be mentioned. The first type is related to specific complications of certain surgical procedures (esophageal anastomosis leakage etc.). The others are anatomic complications encountered during target organ dissection. Postoperative pain secondary to rib retraction and costal margin division should be treated aggressively to prevent pulmonary complications and also to maintain patient comfort. Phrenic nerve injury secondary to diaphragmatic incision is associated with postoperative diaphragmatic dysfunction. Although unilateral diaphragm paralysis is usually asymptomatic, it may cause shortness of breath in patients with impaired pulmonary function. Improper diaphragmatic closure may cause visceral organ herniation. All well-defined complications of thoracotomy and laparotomy are also possible in the thoracoabdominal approach.

Self-study

a. Which are the surgical pathologies requiring a thoracoabdominal approach?
b. What should be the patient's standard position for left thoracoabdominal approach?
c. Which diaphragm incision type is more at risk of phrenic nerve damage?
d. Which vessel should be considered during costal margin dividing?
e. What are the steps in wound closure?

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Thoracotomy as the Surgical Route for Synchronous Thoracic and Non-thoracic Procedures

Achilleas G. Lioulias, Michail D. Tsimpinos and Meletios A. Kanakis

Key Points

- Through a single thoracic incision, surgical access to other anatomic cavities can be obtained. This has the advantage of lesser operational time, lesser surgical trauma and fewer complications.
- Phrenotomy offers excellent surgical access to the underlying ipsilateral upper abdominal organs.
- Under specific conditions, the contralateral lung can be accessed across the mediastinum.
- Malignancy, limited trauma, and non-malignant lesions can be managed through a single thoracotomy.
- Thoracoabdominal incision unifies the major cavities, the abdomen, the thorax, and the retroperitoneal space; it is indicated for locally extended lesions, though it is a highly demanding operation.

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Introduction

The era of modern surgery dictates, smaller and lesser incisions, shorter operational times shorter, hospital stays, lesser complications and better cosmetic results.

There are though many occasions where more than one synchronous operation may be needed, which may include organs in different anatomic cavities or spaces, as for example, a malignancy of the lung and metastasis to the ipsilateral adrenal gland.

The incisions of the classic surgery are usually offered exposure to the target organ or if extended accordingly, they may offer exposure to a wider surgical field or into the same anatomic cavity where the organ-target is located.

However, this is not the case with a thoracotomy; a thoracotomy, despite the excellent surgical exposure of the lung and of the other intrathoracic organs it provides, it also offers excellent exposure to the organs of upper abdomen, and of the contralateral lung too, without the need of extending the initial incision or a second incision [1, 2].

Diaphragm

The diaphragm despite its functional role as a respiratory muscle is the anatomic boundary of the two major anatomical cavities of the human

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body, the thorax, and the abdomen. It preserves at the same time, the different conditions for the proper function of the two cavities, it is the main respiratory muscle and provides anatomic passage of vital organs through its central tendon.

The motor nerve of the diaphragm is the phrenic nerve, which descends on each side of the mediastinum reaching the central tendon and from there spreads to the periphery on the thoracic surface of the muscle. The blood supply of the diaphragm is on the abdominal side. The incision of the diaphragm must be made on the periphery of the muscle, as close as possible to the thoracic wall, where this distal part is actually spared from large nerve and arterial branches. By this incision, the main tendon remains intact, the surgeon avoids surgical maneuvers in proximity to the vital organs, such as the aorta and the heart but, more importantly, damage of the nerve supply of the diaphragm, with consequent dysfunction is eliminated.

The detachment of the diaphragm from the chest wall as proposed by Belsey et al. preserves the phrenic nerve, but its repair by reattachment is more demanding [3]. A circumferential incision of the diaphragm, 2 cm from its chest wall margin has the beforementioned advantage, concerning the preservation of the phrenic nerve and blood supply, but also provides enough tissue length for reconstruction by simple suturing [4].

The length and the position of the incision depend on the organ target. An anterolateral radial incision, on the left hemidiaphragm, provides excellent exposure to the esophagus, stomach, distal pancreas, and spleen; while a

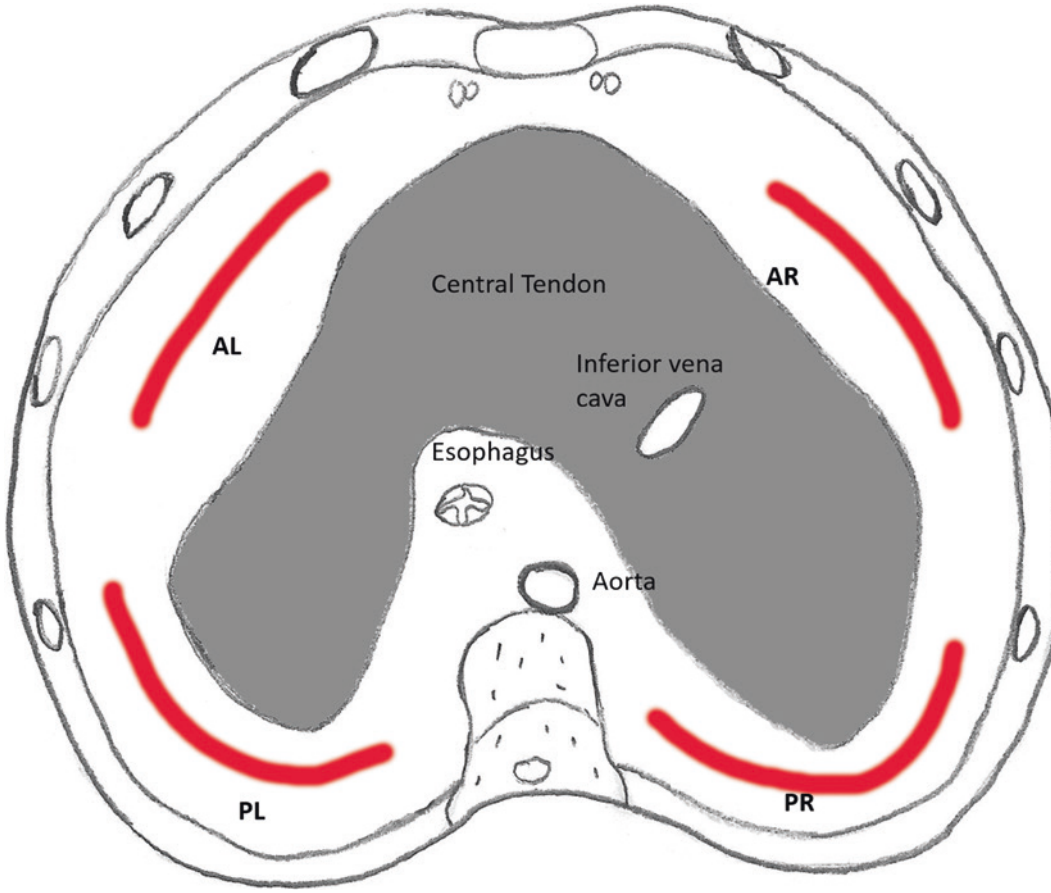

Fig. 1 AL: Antero-lateral left, AR: Anterolateral right
PL: Posterolateral left, PR: Posterolateral right

posterolateral radial incision exposes the kidney, the adrenal glands, and the aorta. On the right side, an anterolateral incision provides excellent exposure to the liver while a posterolateral incision to the adrenal gland, kidney, liver, and inferior vena cava.

It is preferred to start the incision laterally and to extend it accordingly toward the organ target anteriorly or posteriorly correspondingly.

An incision of 7 cm of the hemidiaphragm is usually adequate for exposure and operation of the underlying organ target. In the case, of a retroperitoneal approach, the incision is advised to be started at the level of the vertebral bodies in order, to avoid an inadvertent entrance into the peritoneal cavity (Fig. 1). However, if it is needed such an incision may intentionally be extended anteriorly in order to explore the peritoneal cavity.

This operation can be also performed, without the need of one lung ventilation. At the end of the procedure, the free margins of the diaphragm can be easily approximated by using continuous sutures.

Adrenal Glands and Kidney

The adrenal gland is a common site of metastasis of primary lung cancer. Synchronous or metachronous adrenalectomy provides favorable results, concerning long term survival. After confirming and completing anatomic resection of the affected lung parenchyma, ipsilateral adrenalectomy is possible, without the need of a second thoracotomy [5].

As is already being mentioned, a radial incision is made to the peripheral margin of the diaphragm, 2 cm from the chest wall, from the vertebral bodies anteriorly, in a staged manner in order, to avoid entering accidentally into the peritoneal cavity. On the right side, adrenalectomy is more technically advanced; there the anatomic landmark is the inferior vena cava. The adrenals have single venous drainage; on the right side, the adrenal vein is wide and short that drains directly into the inferior vena cava necessitating increased surgical attention in order, to avoid an avulsion. The dissection of the inferior vena cava should be limited due to its proximity to the thoracic duct. The right adrenal gland is protruding through the retroperitoneal fat and distinguished by the latter by its brown color.

This approach is also valuable in undiagnosed findings of the adrenals since it offers definite diagnosis and treatment [6].

The authors had surgically approached a right lower lobe primary lung tumor and a synchronous primary right kidney tumor through a single thoracotomy incision. The incision was made at the 7th intercostal space and after the completion of the lobectomy the incision was extended anteriorly, the right hemidiaphragm was laterally incised and the thoracic and the retroperitoneal cavities were united. The right adrenal gland was identified and in a staged manner the kidney was recognized too. The procedure completed after the anatomic excision of the kidney.

Liver

The surgical approach of the liver is mainly through an abdominal incision. There are cases though where the transthoracic approach of the liver is feasible.

Liver tumors located in the dome or involve the cavohepatic junction can be easily approache d through this route. Likewise, a case report has been published of a right lower lobectomy of the lung and a posterior superior segmentectomy of the liver with resection of the hemidiaphragm due to primary tumor invasion [7, 8].

Hydatid cysts may concurrently exist in the lung and in the liver too. In case of right lung involvement, after the excision of the lung cysts, liver lesions can be approached and excised through an anterolateral phrenectomy eliminating the need of a second operation [9].

Esophagus and Stomach

Selected cases of esophageal carcinoma can be operated through a single left thoracotomy incision in case the malignancy involves the middle or the lower third of the esophagus.

The operation was first described by John Garlock and Richard Sweet [10]. The incision is performed at the 6–7th intercostal space. The esophagus is then mobilized, and an anterolateral incision is made into the ipsilateral hemidiaphragm. The underlying stomach is excellently exposed. The stomach is mobilized and dissected up to the level where the oncological rules command. The blood supply of the stomach will be from the preserved right gastroepiploic artery. Regional lymph node dissection is performed, and the operation will be completed by the formation of the gastroesophageal anastomosis in the thoracic cavity at the level of the aortic arch. The experienced surgeon will bluntly dissect the duodenum (Kocher maneuver) in order to contribute further to a tension-free anastomosis. Sweet's operation gains popularity and it is considered safe and effective.

The surgical repair of a giant para esophageal is made through a left thoracotomy. Belsey Mark IV operation is completed after the division of the phrenoesophageal ligament and the esophagogastric junction is brought into the left hemithorax though the hiatus [11, 12].

Lung

The access from one thoracotomy to the contralateral lung is challenging but when certain conditions are met, is possible. These conditions are the anatomic distribution of the metastases of the contralateral lung and possibly the presence of adhesions.

It has been already described a successful resection of bilateral lung metastases, from the right upper, middle and left upper lobes through a single right thoracotomy. The left upper lobe is approached, by opening the pleura anterior to the ascending aorta [13]. A single ported thoracoscopic approach has been reported, across the mediastinum, for bilateral metastasectomy [14].

Another possible pathway from the right hemithorax to the left is across the mediastinum behind the posterior pericardium and anteriorly to the esophagus, at the level of the inferior vena cava [2]. The inferior pulmonary ligament is dissected, the left lower lobe is mobilized before excision of the metastases. This access make feasible the palpation of the whole left lung parenchyma for identification of other metastases too (Fig. 2).

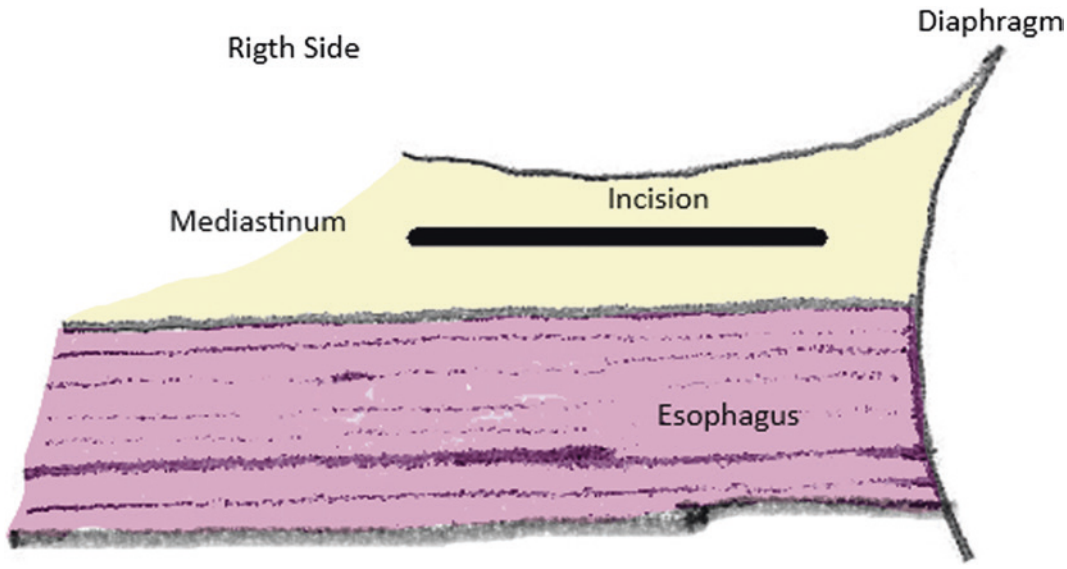

Fig. 2 Place of incision of the mediastinum of the right hemithorax for access of the left lung

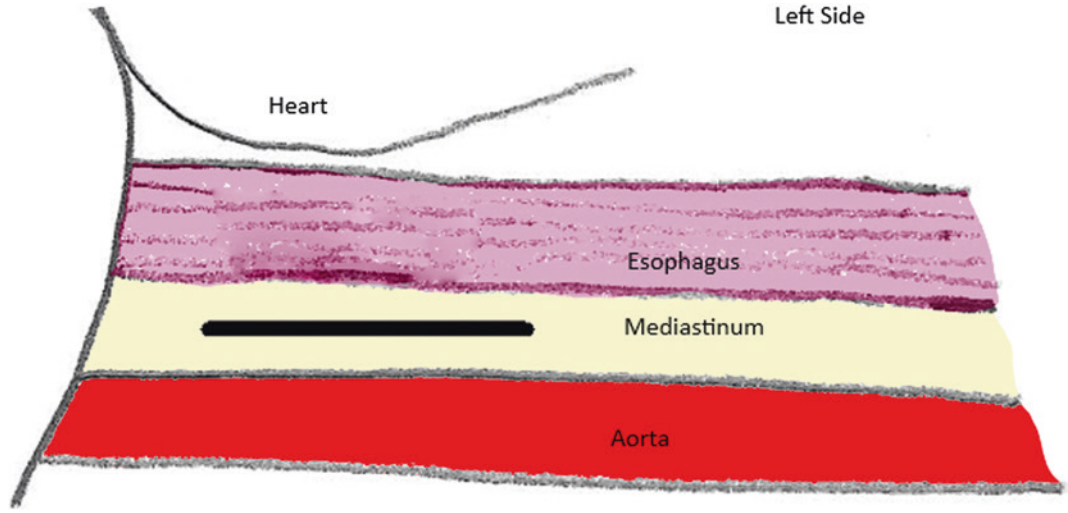

Fig. 3 Place of incision of the mediastinum of the left hemithorax for access of the right lung

Access of the right lung through a left thoracotomy is also achievable; The right pleura extends adjacent to the right aspect of the lower third of esophagus behind the posterior pericardium [11]. The ideal surgical plan of such an approach is by entering the right hemithorax between the aorta and the lower third of the esophagus (Fig. 3).

Proper aerostasis and positive pressure ventilation, of the contralateral field, will efface the need of thoracic tube placement.

The advantage of a single thoracotomy for bilateral lung metastasectomy, is that except it the greater stress of the two thoracotomies, it also eliminates the time interval needed for two consecutive operations to be performed.

Traumatic Injuries, Spleen, Pancreas and Diaphragm

Limited abdominal trauma may be managed wisely by a thoracotomy. The cases of concomitant thoracic and ipsilateral upper abdominal trauma can easily be managed, with a single thoracotomy [1]. Moreover, the thoracic approach offers a direct inspection of the diaphragm in cases, where a diaphragmatic injury is suspected and cannot easily be diagnosed either preoperatively or through an abdominal approach (Photo 1).

Splenectomy can easily be performed through a left thoracotomy and phrenectomy and is ideal when accompanied by an injury of the left lung or hemidiaphragm (Fig. 4). With this approach, the hilum of the spleen is accessible as well as the short gastric arteries and the tail of the pancreas. With a left phrenectomy, the lower abdomen and the contralateral upper abdominal organs are not accessible. This approach offers to the trauma patient the option of a shorter in time operation, and the advantages of the one surgical incision.

Splenectomy, through a thoracotomy, can be used also for elective cases as for hematological disorders. Klimaskii et al. published 226 such cases and noticed fewer postoperative complications when compared to the abdominal approach.

Left anterolateral phrenectomy, provides an excellent and safe surgical approach to the spleen and the ipsilateral upper abdominal organs. It can be used either for trauma or for other disorders too [15].

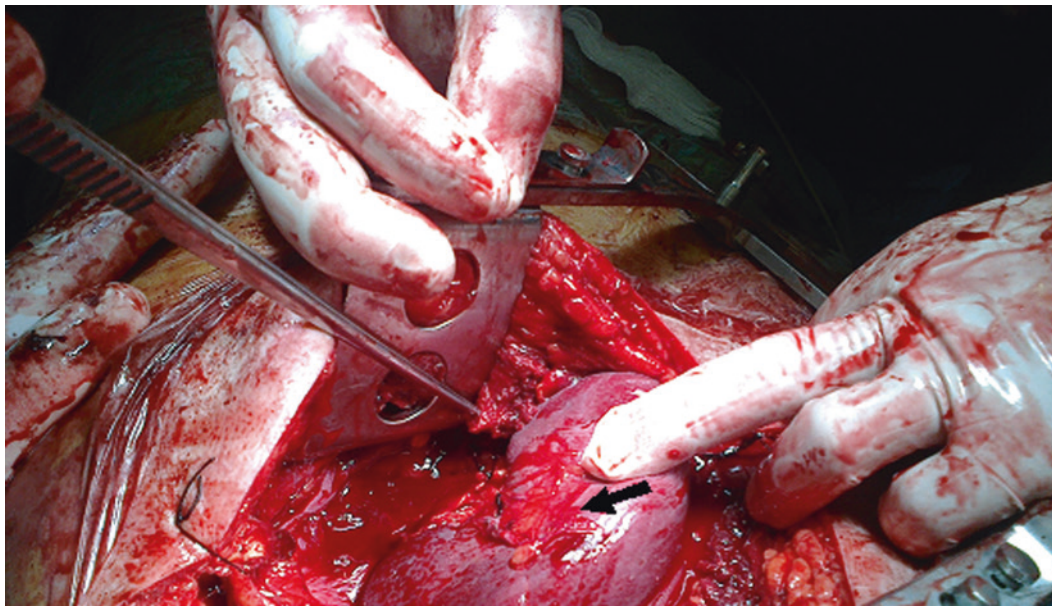

Photo 1 The spleen

Thoracoabdominal Incision

The thoracoabdominal incision provides excellent exposure concomitantly to the thoracic, abdominal and retroperitoneal space. The lower esophagus, the gastroesophageal junction, the stomach, the left hemidiaphragm, the distal pancreas and spleen, the left kidney and adrenal gland, and the aorta, are approached through the left side. The upper esophagus, the liver, and inferior vena cava, the proximal pancreas, the right hemidiaphragm, the right kidney, and the adrenal gland, are approached with a right thoracoabdominal incision [16].

Technically, the thoracoabdominal incision is highly demanding concerning the surgical skills; there are multiple points where special attention is mandatory in order, to avoid an accidental splenic injury, phrenic nerve injury, ureteric injury, left first lumbar vein injury.

The patient's position is very important; the abdomen is tilted at 45 degrees while the thorax is in a completely lateral position, with this position maximal access to both of the major cavities, is achieved [17, 18].

The oblique abdominal incision is made first, the abdominal wall muscles are divided, and the rectus muscle and sheath are dissected laterally. The costal arch is separated between the 7th and 8th intercostal space in order, to connect the abdominal with the thoracic incision. The diaphragm is circumferentially divided at its periphery, 2 cm from the chest wall, to facilitate its closure as mentioned earlier. For thoracoabdominal incision, one lung ventilation is not mandatory [19].

With this incision complex tumors with local extended invasion of the liver or kidney are made possible due to its excellent exposure and the actual unification of the two cavities, the abdominal and the thoracic [20, 21]. Even more complicated operations may be performed, with thoracoabdominal incision, requiring cardiopulmonary bypass (CPB) with peripheral cannulation and hypothermic circulatory arrest [22].

Distal esophageal carcinoma can be operated with a left thoracoabdominal incision providing, excellent exposure and at least two field lymph node dissection.

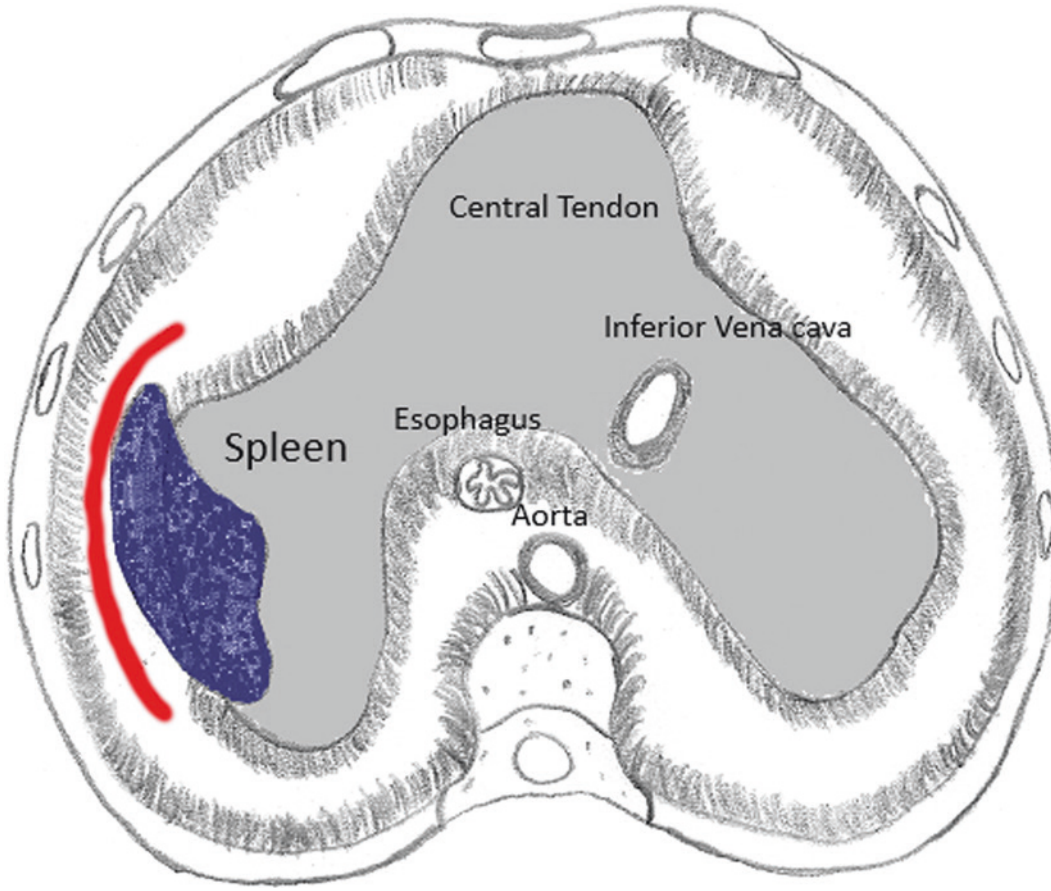

Fig. 4 Phrenic incision for spleen exposure

The thoracoabdominal incision is demanding very good knowledge of anatomy, by the surgeon, for the opening and closure; it is not indicated for children; under these circumstances it is comparable in pain, hospital stay and return to normal activities with the abdominal incisions [23].

Self-study

1. The distribution of the branches of the phrenic nerve on the diaphragm is:
   a. On the abdominal side of the diaphragm.
   b. An incision in the periphery of the diaphragm is safer concerning the nerve damage.
   c. Distributed more densely in the periphery of the muscle.
   d. None of the above is correct.
2. The adrenals:
   a. The right adrenal gland cannot be reached through phrenotomy.
   b. The proper incision for surgical exposure of the left adrenal is the anterior phrenotomy.
   c. The incision of the diaphragm should be in staged manner from the vertebral bodies to the lateral margin of the muscle.
   d. Adrenalectomy through a phrenotomy is indicated only in benign lesions.
3. An anterolateral incision of the left hemi-diaphragm provides exposure to the following abdominal organs.
   a. The Stomach, the head of the pancreas, the spleen, the duodenum
   b. The liver, the left adrenal, and the cardia.

c. The Left kidney.
d. The spleen, the stomach, the tail of the pancreas.

4. Trauma:
   a. Lower abdominal trauma can be managed by a phrenotomy.
   b. Upper abdominal organ limited trauma can be managed by a phrenotomy.
   c. Major upper abdominal organ trauma ca be managed by a phrenotomy.
   d. Rupture of the diaphragm is always associated with abdominal trauma.

Answers

1. b = Correct. The branches of the phrenic nerve are more sparse in the periphery of the diaphragm thus an incision at the lateral margin is safer.
2. c = Correct. The adrenal is reached through a posterolateral incision of the diaphragm in order to avoid large branches of the phrenic nerve and to access the retoperitoneal space.
3. d = Correct. The spleen, the stomach, the tail of the pancreas are accessible in the left upper abdomen.
4. c = Correct. Only limited trauma of the underlying upper abdominal organs can be managed through a phrenotomy.

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One Stage Minimally Invasive Thoracoscopic Lung Resection and Transphrenic Adrenalectomy: Surgical Technique

Patrick Bagan, Bassel Dakhil, Rym Zaimi, and Mahine Kashi-dakhil

Key Points

1. Approximately half of all patients diagnosed with NSCLC, at the same time, present metastatic diseases.
2. In selected oligometastatic patients with N0 non-small cell lung cancer, locally aggressive therapies given with the intent of eradicating all sites of known metastatic sites could result in long-term survival, or even cure.
3. Key determinants of long-term survival of oligometastases in NSCLC patients include lower nodal stage, adenocarcinoma histology and aggressive therapy to the primary tumor.
4. A transdiaphragmatic approach provides excellent exposure to the adrenal gland with no excess postoperative morbidity in this small subset of patients with resectable primary lung cancer.

Metastasis from non-small cell lung cancer (NSCLC) is traditionally considered as a contraindication to surgery. Favourable long-term survival following staged lung resection and resection of synchronous isolated adrenal metastasis has been reported in N0 patients [1, 2]. Considering the retroperitoneal location of the adrenal gland, the transdiaphragmatic approach [3] offers an attractive alternative to standard approaches to adrenal tumours. We describe a technique of simultaneously completing a curative lobectomy and adrenalectomy safely and effectively through the thoracic approach.

Technique

Patients benefit of a clinical work up with fiberoptic bronchoscopy, thoracic, upperabdominal CT scan, systematic PET scan, mediastinal endobronchial ultrasound (EBUS) guided fine needle aspiration and MRI of the brain to exclude N2 disease or other distant metastases.

Preoperative functional evaluation consists of spirometric and plethysmographic tests, diffuse lung capacity (DLCO) and arterial blood gas measurement. Multidisciplinary lung cancer committee generally proposes first line surgical treatment. Our technique is inspired by the single incision approach [4].

VATS approach is performed through four thoracoports for optic (10 mm in diameter) and for endoscopic instruments (3, 5 and 10 mm in diameter) placed in the sixth intercostal space on the anterior axillary line, on the seventh intercostal space on the mid-axillary line and posteriorly to the scapula in the auscultatory triangle in the sixth intercostal space (Fig. 1).

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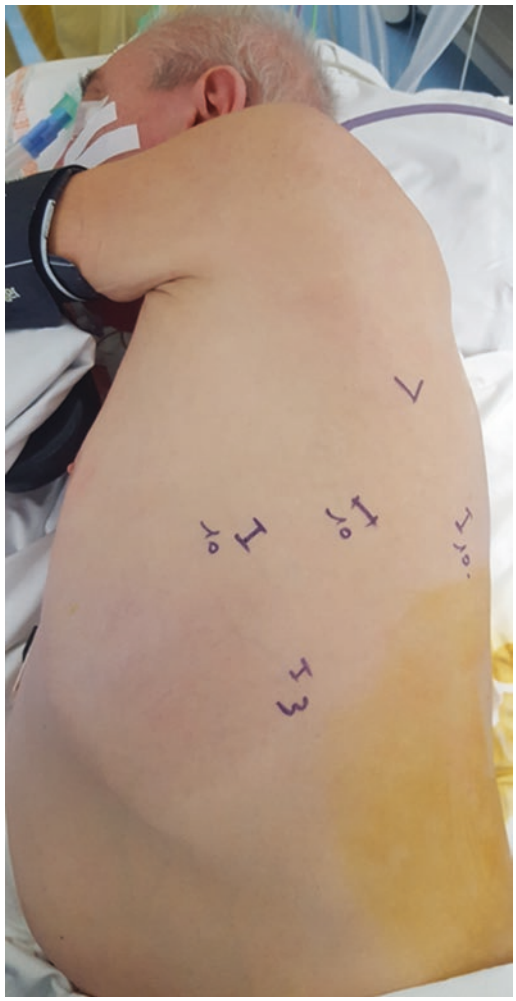

Fig. 1 VATS approach for adrenalectomy and lobectomy

Transdiaphragmatic approach is performed through the four ports with a low pressure capnothorax. Phrenotomy is started from the mediastinum and then extended posteriorly with the advanced bipolar device. The peritoneum and retroperitoneal fat are exposed with 3 mm instrument (Fig. 2). Meticulous division of the arteries and venous drainage ligation was performed with the bipolar device to avoid bleeding (Fig. 3). The adrenal gland is extracted en-bloc through the 10 mm incision (Fig. 4). Hemostasis is completed with instillation of hemostatic glue in the adrenalectomy bed and the diaphragm is closed using interrupted stiches.

A VATS lobectomy is then performed with hilar and mediastinal lymphadenectomy.

The pain control is obtained with a paravertebral catheter inserted in the seventh intercostovertebral space. The catheter is removed at the same time of the chest tube removal. The patient is discharge at home with paracetamol and a nonsteroid anti-inflammatory drugs regimen which is continued during physiotherapy.

Comment

The solitary adrenal metastases are often on the same side as the primary lung lesion. This suggests a physiological significance of diaphragmatic lymph vessel connections between the lung and the retroperitoneum and a relationship between ipsilateral adrenal metastases and limited metastatic spread [5]. A durable long-term survival is observed in approximately 25% of patients following adrenalectomy for synchronous and metachronous metastasis from NSCLC [6]. In oligometastatic NSCLC patients, meta-analyseses suggest that aggressive therapies in the primary lung cancer, the (y)pT-stage, the absence of nodal diseases and the adenocarcinoma histology have been clarified as positive prognosis [7]. For the subgroup of NSCLC patients with isolated adrenal metastasis undergoing surgical treatment for the primary tumour and adrenal metastasis could achieve a significant survival benefit, especially if they are negative for lymph node metastasis [8]. Patients with ipsilateral adrenal metastasis may derive the greatest survival benefit from adrenalectomy, since spread to the ipsilateral gland may occur via direct lymphatic channels in the retroperitoneum. Involvement of the contralateral adrenal may signify haematogenous spread and therefore, a more aggressive process [9].

The VATS approach is an alternative approach to the double thoracotomy technique [4] and to the laparoscopic adrenalectomy. This approach is a viable option for the treatment of this difficult problem with potentially less morbidity. The major issue of this approach for adrenalectomy is the vessel closure. The advance bipolar device is used because of its

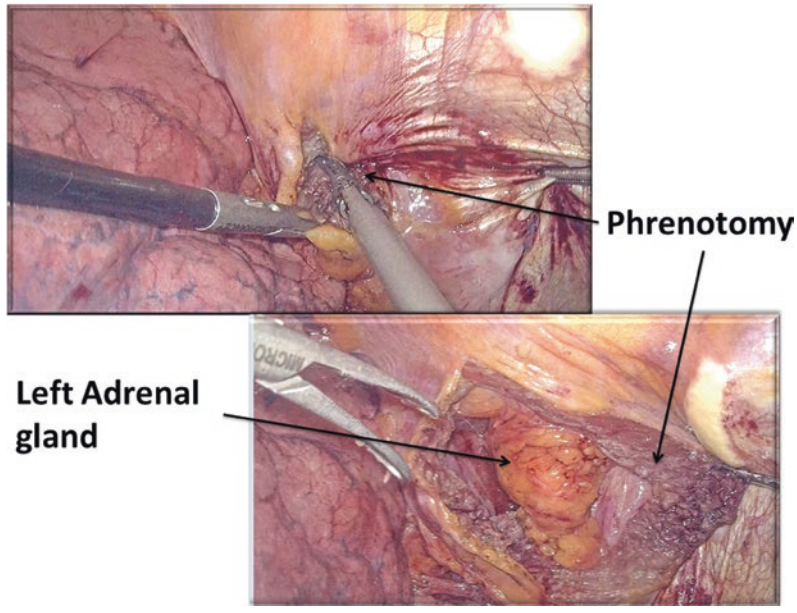

Fig. 2 Left phrenotomy for the exposition of the adrenal gland

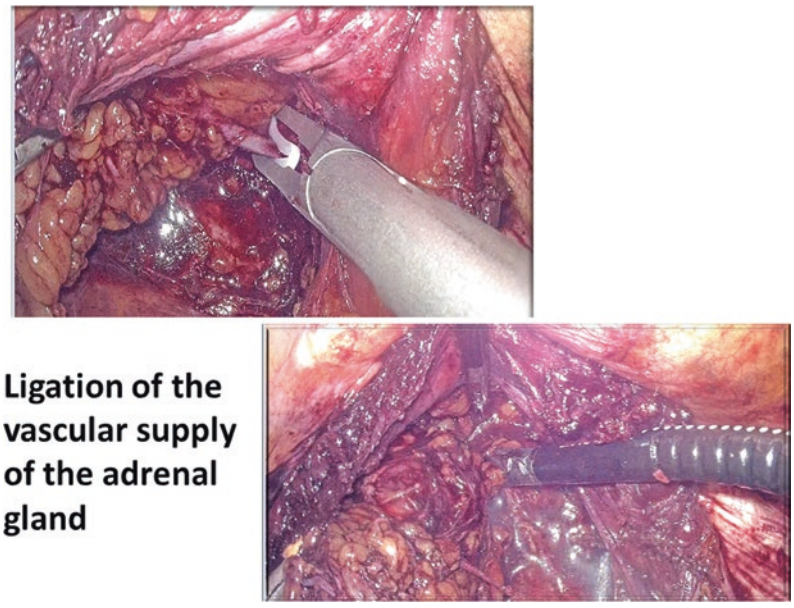

Fig. 3 Vascular ligation of the adrenal gland

safety and efficacy for hemostasis during adrenalectomy [10].

In conclusion, adrenalectomy should be considered as a therapeutic option for patients with synchronous metastases from NSCLC. Adrenalectomy can be carried out during the same operation. The minimal invasive technique should be the preferred approach in this small

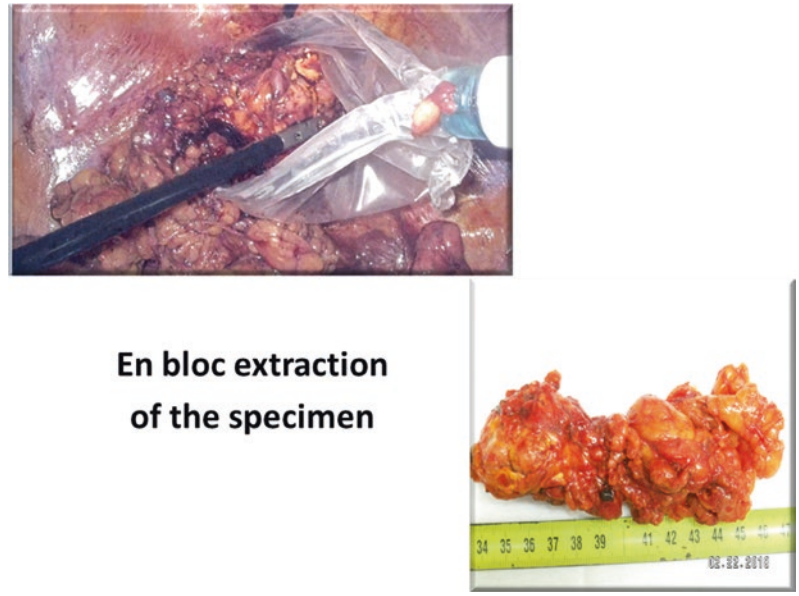

Fig. 4 En bloc extraction of the adrenal gland

subset of patients with resectable primary lung cancer.

Compliance with Ethical Requirements

P. Bagan, B. Dakhil, R. Zaimi, M. Kashi-Dakhil declare that they have no conflict of interest.

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Anterior Surgical Approach to the Abdominal Aorta

Delfina Fletcher-Sanfeliu, Alberto Domenech Dolz, Álvaro García-Granero, Ivan Martin-Gonzalez, and Gianluca Pellino

Key Points

1. The abdominal aorta can be approached via several routes.
2. Knowledge of anatomy and anatomic landmarks is vital to avoid inadvertent injuries to vessels and surrounding organs.
3. There is no ideal approach, rather it should be based on specific characteristics of the disease, presentation, surgeon preference and ability, and patient shape.

Introduction and Anatomy

The aorta enters the abdominal cavity through the diaphragmatic hiatus. Its upper limit lies at the height of T12 (Fig. 1).

Postero-anteriorly toward the thorax, two lumbar lymphatic trunks can be identified posterior to the aorta, which direct toward the satellite lymphatic nodes of the abdominal aorta. Intestinal lymphatic drain into the left para-aortic trunk. These two lumbar trunks can seldom connect caudally to the aortic hiatus, forming a pouch: the chyle cistern, which corresponds to the origin of the major thoracic duct. The tributary veins of the azygos vein or of the left inferior hemiazygos vein run through the same diaphragmatic orifice. The sympathetic nerves run down posterior to the arcuate ligament and anterior to the psoas muscle. The inferior phrenic arteries originate from the coeliac aorta and vascularize the diaphragm.

The abdominal aorta runs slightly on the left of the median line until L4 or L5, at which height it bifurcates into common iliac arteries (aortic bifurcation). The latter split to form the internal and external iliac arteries. The autonomic nervous plexus is intimately related with the aorta along its entire length (Fig. 2).

Visceral arteries originate from the abdominal aorta. The origin of the renal arteries is usually used as landmark between supra-renal and infra-renal abdominal aorta.

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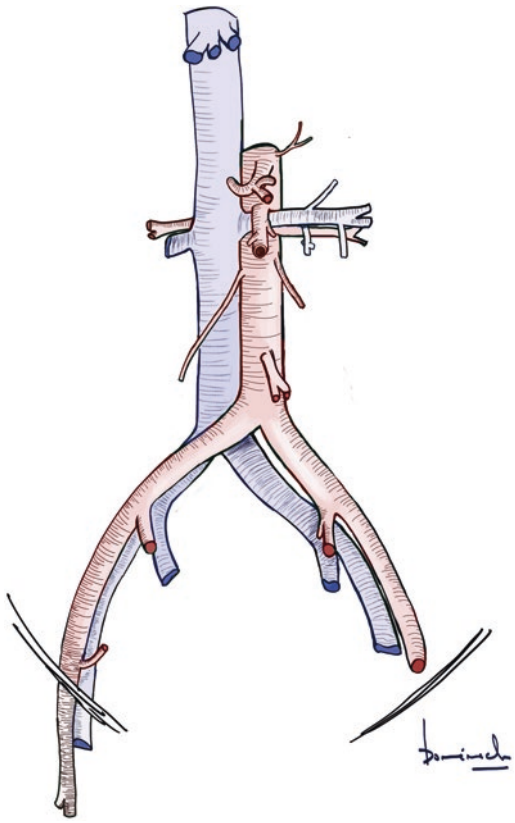

Fig. 1 Abdominal aorta and inferior vena cava. Left and right renal vessels, visceral arteries: celiac trunk, superior mesenteric artery, inferior mesenteric artery, left and right iliac vessels

This site is also limited by the left renal vein crossing anteriorly the aorta in 90% of individuals. In the remainder 10% of cases the left renal vein can be retro-aortic or form a venous collar surrounding the aorta (Fig. 3).

The coeliac trunk (CT) and the superior mesenteric artery (SMA) originate from the sub-diaphragmatic aorta, in the segment which is most difficult to access. The inferior mesenteric artery (IMA) originates at the level of the infra-renal aorta, and it can be accessed directly in a site which is familiar to cardiovascular surgeons, even if it rarely requires reconstruction or revascularization.

The CT originates from the anterior wall of the aorta at the level of T12-L1. After 2–3 cm it crosses the superior border of the pancreas, where it splits into three branches: the hepatic artery, the left gastric artery, and the splenic artery (which is the longer). The origin of the CT is surrounded by lymph nodes and nervous fibres from the solar plexus. It is covered by the posterior parietal peritoneum and can be covered by the superior border of the pancreas.

The SMA is the longest artery of the visceral trunks. It feeds the pancreas, the small bowel, and the right half of the colon. It originates from the anterior wall of the aorta approximately 1 cm caudal to the CT. Proximally, SMA presents a fixed supra-mesenteric segment which is difficult to be accessed and is often revascularized in the event of atherosclerotic stenosing lesions. The SMA is often exposed more distally, in the intra-mesenteric segment, in order to treat mesenteric embolism. In its fixed segment, the SMA is initially retro-pancreatic (first 2–3 cm).

The left renal vein divides posteriorly the SMA from the aorta. In this segment, the SMA is surrounded by nervous fibres from the aorto-mesenteric plexus, similarly to the CT. Then, the artery runs between the inferior border of the pancreas and the third duodenal portion (Fig. 4). The inferior mesenteric vein runs on its right. On its left, the ligament of Treitz suspends the duodenojejunal flexure from the left diaphragmatic pillar.

Before reaching the free intra-mesenteric segment, the SMA runs anterior to the duodenum, covered by the sub-mesocolic posterior parietal peritoneum. At this level, an infrequent right hepatic branch can originate from the SMA in 8–15% of individuals. This artery runs posterior to the pancreas and the portal vein. The superior right colic artery, which is one of the longest branches, originates from the first segment of the SMA and runs transversally towards the right. The right colic, the jejunal and the ileal arteries originate from the free intra-mesenteric segment of the SMA (Fig. 5).

Important anastomoses of the mesenteric arteries are present in the coeliac, superior and inferior mesenteric territory. Connections between CT and SMA occur via the anastomotic network of the duodenal pancreatic block.

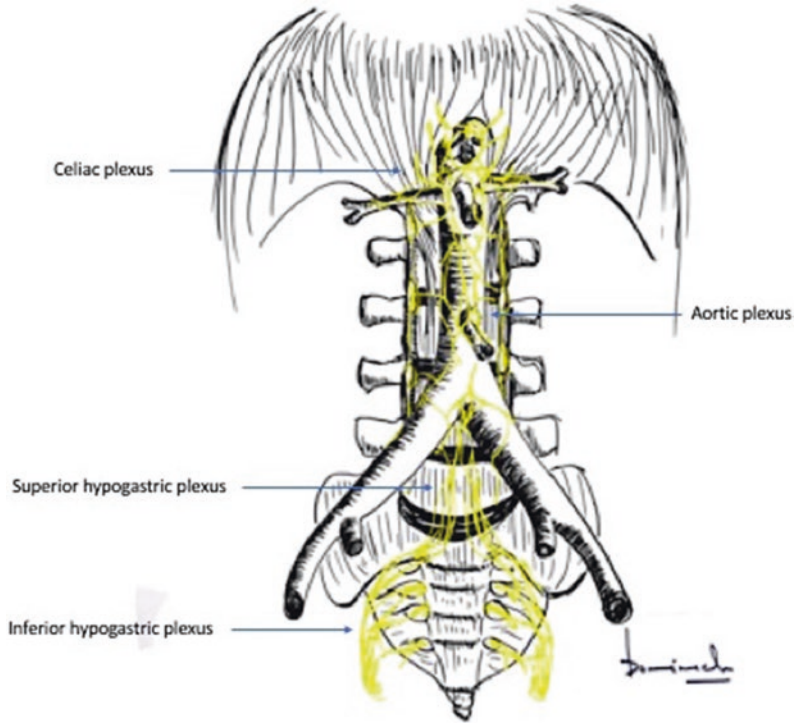

Fig. 2 Autonomic nervous plexus

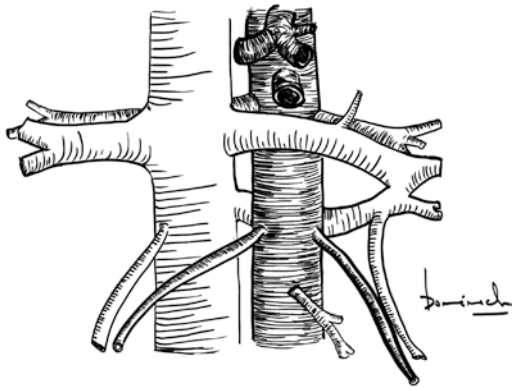

Fig. 3 The left renal vein crosses anteriorly the aorta in 90% of individuals. In the remainder 10% of cases the left renal vein can be retro-aortic or form a venous collar surrounding the aorta

Connections between SMA and IMA occur via paracolic anastomoses. The IMA territory and the hypogastric arteries are connected by means of hemorrhoidal arteries (Fig. 6).

If one of these anastomoses is prominent, it should raise suspicion of an occlusive disease in one of the visceral trunks.

Renal arteries are located dorsally, practically contacting with the posterior abdominal wall, which makes accessing them difficult. They normally originate one at each side of the aorta, from the lateral wall of the abdominal aorta; each artery runs obliquely, postero-laterally, and down toward the renal hilum. At the level of the renal hilum, the artery constitutes the most dorsal structure, and it is covered anteriorly by the renal vein. On the right side, the right renal artery (before connecting with the renal hilum) shows a long segment covered by the inferior vena cava and, more ventrally, by the second duodenal portion and head of pancreas (which could be retracted towards the right during the trans-peritoneal approach). On the left side, the left renal artery is part of the renal hilum in its entire length. It is covered anteriorly by the left renal vein, by the body and tail of the pancreas,

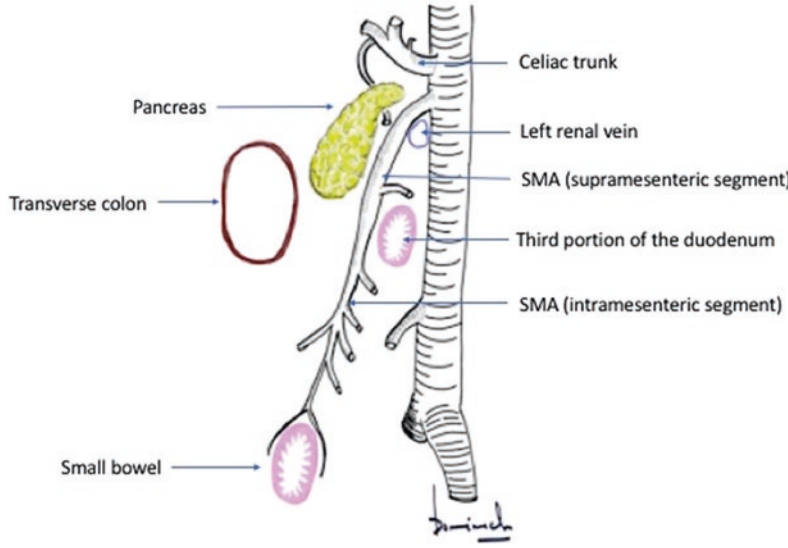

Fig. 4 Superior Mesertic Artery (SMA) route and its relations with other structures

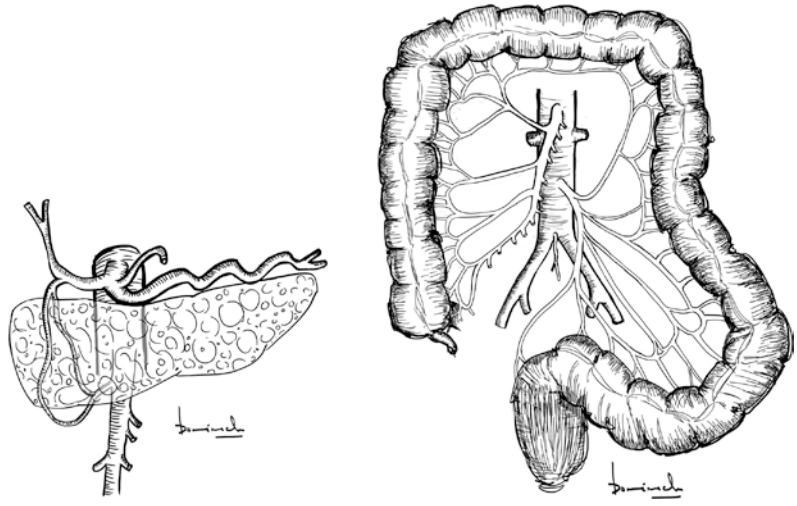

Fig. 5 Different arteries originated from celiac trunk, superior mesenteric artery and inferior mesenteric artery

by the omental sac, and by the stomach. These factors make a transabdominal approach more difficult.

Renal arteries originates at the level of L1–L2, with some individuals variations (the higher their origin, the more difficult is exposing them). Anatomical variations exist in terms of number of renal arteries in up to 25–30% of cases.

The IMA originates from the anterior wall of the infra-renal aortic segment, which is located between the upper limit of L2 and the lower limit of L4. Many lumbar arteries originate from the posterolateral wall on both sides of the aorta. The medial sacral artery originates at the level of the aortic bifurcation. Lumbar vessels (artery and vein) can be found on the posterior wall of the aorta and the vena cava, between the lumbar vertebrae and the psoas muscle.

The inferior vena cava usually runs on the right side of the aorta. In 0.2–0.5% of the

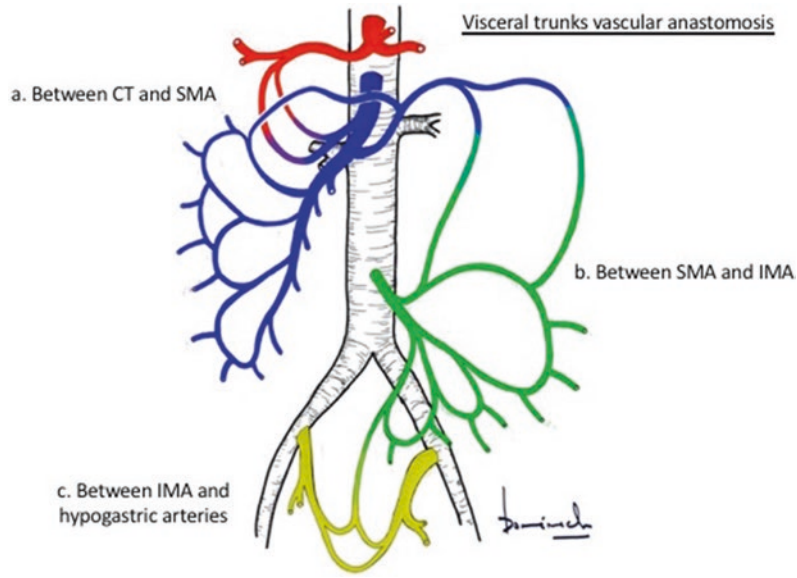

Fig. 6 Anastomoses between visceral trunks: **a** Between CT and SMA. **b** Between SMA and IMA. **c** Between IMA and hypogastric arteries. CT: Celiac Trunk, SMA: Superior Mesenteric Artery, IMA: Inferior Mesenteric Artery

individuals a left inferior vena cava can be identified, which crosses from left to right the anterior wall of the aorta at the level of the renal arteries.

Lastly, the common iliac arteries originate after the aortic bifurcation. The latter is divided at the level of L4 by the left common iliac vein, which crosses from right to left posterior to the right common iliac artery. Iliac vessels run along the medial surface of the psoas muscle, with the genitofemoral nerve running over its surface and the femorocutaneous nerve lying lateral to it. The ureters and the gonadal vessels are located parallel to the aorta and inferior vena cava, ureters being more lateral.

Preoperative and Preanaesthetic Considerations

Over the following chapter we will be dealing with abdominal aorta aneurisms, however the described principles apply also to ischemic disease of the aorta and of the visceral trunks.

The transabdominal repair of an aneurism is a major surgical procedure, which brings about the risk of causing life-threatening lesions during different steps of the intervention. An even minimal error in a single detail of the procedure can result in serious consequences. A meticulous attention to detail is therefore warranted.

When dealing with diseases of the abdominal aorta, it is important to mention Type IV thoracoabdominal aneurisms (TAAA) of the Crawford (Fig. 7), which account for<25% of all TAAA. They do not strictly fit in the definition of thoracoabdominal aneurisms, but they involve the entire abdominal aorta, including the visceral aorta.

In the event of Type IV TAAA, distal aortic perfusion is not usually justified, making the repair of these aneurisms simpler compared with other TAAA. In experienced hands, the duration of expected visceral ischemia should be short. The risk of spinal damage is also lower, because the artery of Adamkievicz usually originates more proximal to the upper limit of these aneurisms.

However, devastating complications can occur, especially those related with the duration of intestinal, renal, and spinal ischemia, which could be more apparent in patients with preexisting cardiac or renal comorbidities.

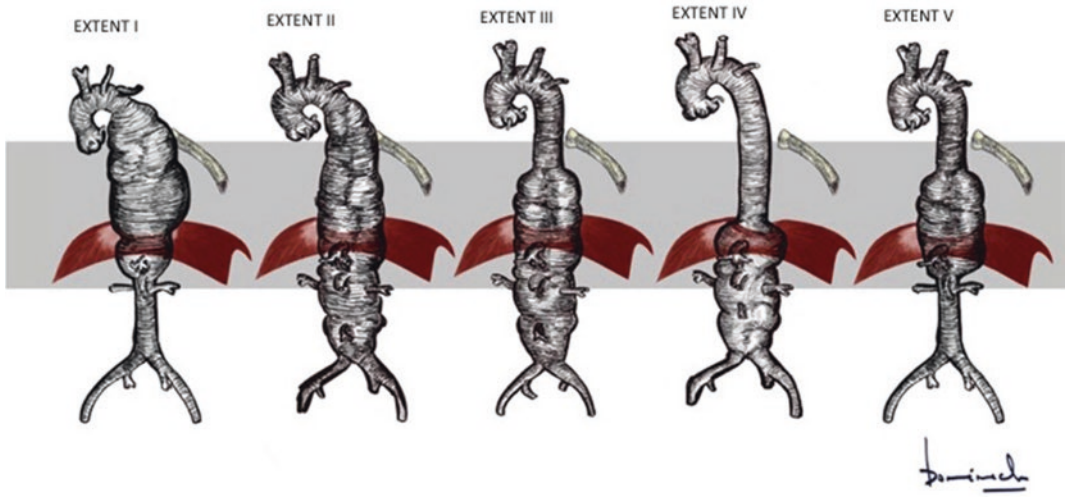

Fig. 7 Thoracoabdominal aneurisms of the Crawford classification

With the exception of emergency cases (which are assessed with CT-angiography alone), all patients needing management in elective setting a complete vascular assessment can be obtained, including doppler ultrasonography (US) of the supra-aortic trunks, CT-angiography of the thoracoabdominal aorta, and—when the suspicion of stenosing lesions of visceral arteries exists—antero-lateral angiographic scans of the proximal abdominal aorta. A spinal angiography can be advocated in selected cases.

A preoperative assessment of cardiac, respiratory, renal and neurologic function is mandatory. Coronary angiography is reserved for patients with clinical symptoms of ischemic cardiopathy or in those with positive stress-test (dobutamine-echocardiography or cardiac MR). Selective intubation is not required. Cerebrospinal fluid is only tested if arteriography showed that the artery of Adamkievicz is located in the critical area of the aneurism.

During aortic clamping, the rapid and relevant increase of the afterload must be correctly managed, requiring continuous monitoring of arterial blood pressure by means of a radial arterial line and vasodilating agents or inhalation anaesthetics. Special attention must be paid in patients with cardiopathy, who might benefit from a distal aortic perfusion via a partial cardiopulmonary bypass, a left heart bypass or a passive shunt, in order to contain the cardiac consequences of aortic clamping.

After the clamping, the induced hypovolemia and vasodilatation related with the ischemia-reperfusion syndrome requires a specific management of the cardiac output and the blood pressure, which implies temporarily using vasoconstricting agents.

Another peculiar consideration of Type IV TAAA is represented by the need of compensating extensive blood loss, which requires rapid transfusion of blood products. Hence, the latter should be promptly available, even if it is difficult to estimate preoperatively the required quantity of these products. A cell-saver suction device could be useful under these circumstances to allow rapid autotransfusion.

It could be useful to monitor cardiac output and pre-load with dedicated systems (e.g. Swan-Ganz). The global parameters of oxygenation (SvO^2) are also part of the monitoring. Intraoperative ventricular dysfunction can be assessed by means of transoesophageal US (TEE).

Lastly, perioperative optimization of oxygen transport (combination of cardiac output and haemoglobin) has been directly associated with postoperative outcome. Similarly,

patient-adjusted management of cardiac output and haemoglobin represent key factors to reduce overall postoperative complications, including extra-cardiac events.

Transperitoneal Approaches

The patient is placed in supine position with the arms open (90°) and accessible to the anaesthesiologists.

A cylindric inflatable pillow is placed below the inferior angle of the scapulae, otherwise a flexible operating table can be used. A thermic cover is for the thorax, arms, and legs. The entire abdomen and both groins must be covered within the surgical field. The operating surgeon stands on patient's right, with two assistant on the opposite side.

Median Laparotomy

A median xifo-pubic incision is made, separating the fascia insertion sites of the rectus abdominis muscles (Fig. 8).

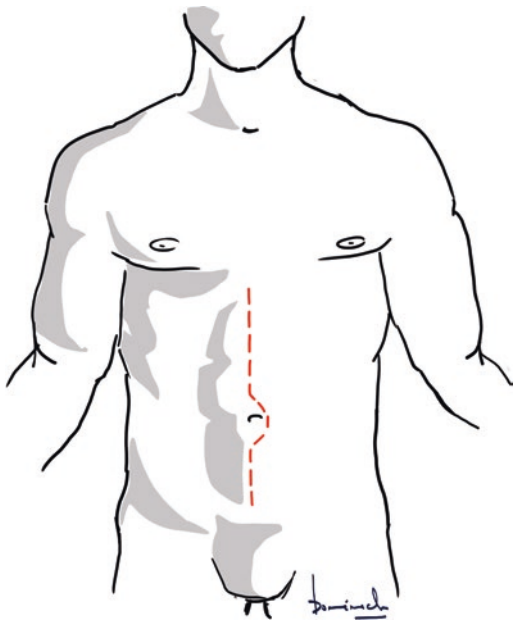

Fig. 8 Median xifo-pubic incision

Incision begins at the xyfoid and is carried downwards on the midline, continuing on the left of the umbilicus until reaching the symphysis pubis.

The subcutaneous tissue is entered at the linea alba at the umbilicus, deepening the incision until reaching the peritoneum.

In very obese patients in whom the linea alba can be difficult to identify, it can be useful to apply lateral traction of the subcutaneous fat on both sides in order to separate it and reveal the linea alba (Fig. 9). The latter must be freed from the fat at least by 1 cm in width, so that the borders can be easily identified at the time of abdominal closure. Haemostasis must be maintained during the opening phase.

The linea alba is opened on the median line, thereafter the preperitoneal fat is opened to expose the peritoneum.

☒ In reoperative surgery, it is useful not to deepen much the incision with the scalpel due to possible adhesions. Using Kocher forceps to lift up the aponeurosis and exploring the peritoneum through the incision with a finger are useful manoeuvres to reduce the risk of visceral injuries.

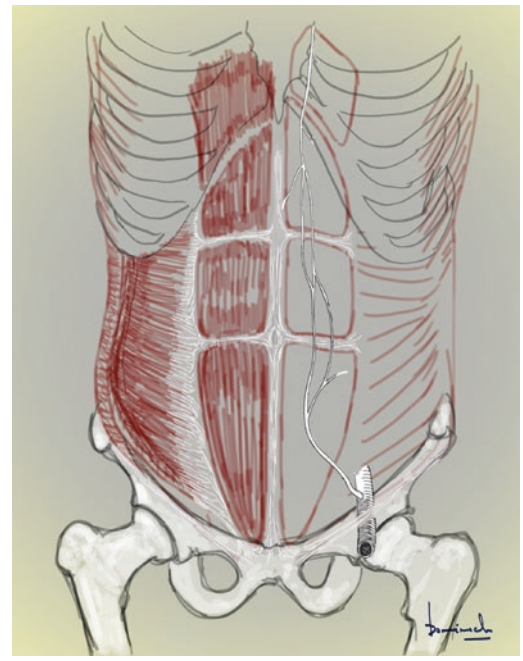

Fig. 9 Abdominal wall muscles, linea alba and epigastric artery

The distal incision of the peritoneum must be close to the bladder, which can be identified following the urachus from the umbilicus to the bladder itself that can be palpated as a fat bulge.

Sometimes smaller incisions can be a better option, depending on the patient and the surgical procedure to be performed. At the same time, an inadequate incision can make the procedure more difficult and longer.

An autostatic retractor can be useful if this incision is performed. The easiest option is to use a retractor which has valves that can separate the margins of the incision, combined with a subcostal retractor that can widen the opening upwards, eventually improving the exposure. It is useful to protect with gauzes the abdominal borders where the valves will be placed. Ideal retractors are those with different valves, allowing to separate the abdominal wall and viscera (e.g. Omnitrac©).

Closure of the Laparotomy: It is useful to pick both sides of the aponeurosis of the rectus abdominis muscles with two Kocher forceps in order to better identify them. Similarly, the upper and lower border must been adequately exposed, displacing the fat tissue in order to place the first stitch. Both absorbable and nonabsorbable sutures can be used. Both single stitches closure and (more frequently) running suture with a loop stitch can be adopted to approximate the peritoneum and the anterior aponeurosis. This suture is facilitated if the assistant surgeon lifts the Kocher forceps in so that the viscera are clearly separated from the aponeurosis. Usually, two entire loop sutures are used, passing the stitches at intervals of 1–2 cm and ensuring an adequate amount of aponeurosis is caught. When reaching the end of the suture line, it becomes difficult to see the inside of the abdomen, therefore placing the back of a forcep inside the defect and passing the stitch between this and the wall can help avoiding inadverteng bowel injuries.

After closing the fascia, some surgeons use to reapproximate the fascia of Scarpa, others close the subcutaneous tissue with absorbable 3/0 stitches, and some close the skin only (either with staplers, subcuticular running suture or nonabsorbable single stitches).

In selected patients at high risk of postoperative evisceration (advanced age, malnutrition, immunodepression, wound infection, high intra-abdominal pressure, prominent abdominal obesity) a suture with entire-wall stitches. A size 2 nonabsorbable suture is used with a big needle, which is able to pass all the wall planes but the peritoneum, aiming to leave the suture in the preperitoneal space rather than contacting with the small bowel. Some surgeons advocate the use of rubber tubes through which sutures are passed and left on the surface to avoid damaging the skin. These should not be tied with excessive tension because of the postoperative oedema (it should be possible to pass a finger between the suture and the abdominal wall). Sutures are often left in place for three weeks.

Median laparotomy is the technique of choice to approach the abdominal aorta.

☑ It allows for the incision to be extended cranially and, if needed, it permits clamping the supra-celiac aorta via the lesser sac. It allows caudal access to both iliac vessels. It also allows control of visceral arteries with variable difficulties.

☑ It is the technique of choice in the event of emergencies needing assessment of the lesions which was not possible preoperatively.

☒ However, it is associated with relevant respiratory complications, with up to 50% reduction of the vital capacity.

☒ The evisceration of bowel caused by the longitudinal infra-mesocolic approach can affect intraoperative hemodynamic stability and increases the rates of postoperative ileus.

☒ Lastly, it results in a significant number of long-term abdominal wall hernias.

☒ Transperitoneal approaches should be avoided in obese patients with an hostile abdomen, those with a colostomy and those with urinary diversions.

Chevron

The patient is placed in supine position with the arms open and the cylindric inflatable pillow at the level of the lumbar region.

Chevron incision consists of a bilateral subcostal access (Fig. 10). It runs 4–5 cm above the umbilicus and offer access to the entire abdominal cavity. The subcostal incision is carried out 2 cm lower than the costal arch and can be extended toward the midline or to posterior axillary in the lumbar region. This incision is well tolerated in terms of respiratory function and rarely causes hernias or eventrations.

If needed, it can be extended upwards with an additional cut on the midline, going beyond the xifoid.

The following structures will be encountered: the anterior aponeurosis of the external oblique muscle, the rectal muscle, the posterior aponeurosis of the rectal muscle, the peritoneum, and, laterally, the internal oblique and transverse muscle, and the peritoneum. It is important to identify and ligate both epigastric arteries, which runs between the venter of the rectal muscles and their posterior aponeurosis.

Once the peritoneal cavity has been entered, the round ligament is ligated and a minimal mobilization of the falciform ligament is performed, until identifying the structures described later in the "supra-mesocolic approach" section (Fig. 11).

In order to ease the retraction of the inferior abdominal wall and to improve view, silk stitches can be placed to fix the aponeurosis to the pubis. Retractors can be used.

☑ Compared with midline laparotomy, Chevron incision provides better exposure of the supra-mesocolic compartment, as well as medial visceral rotations described later. Moreover, it allows good access to the visceral vessels and iliac vessels. It is often used in liver surgery.

☒ On the other hand, it requires longer time to be performed than median laparotomy, which makes it less suitable for vital emergencies.

If required, the incision can be extended upwards on the midline to go higher than the xifoid. This variant is known as "Mercedes-Benz" incision (with xifoid resection) in order to optimize the surgical field at the level of the supra-celiac aorta. It can be prolonged to become a partial inferior sternotomy, opening or not the pericardium. The diaphragm can be

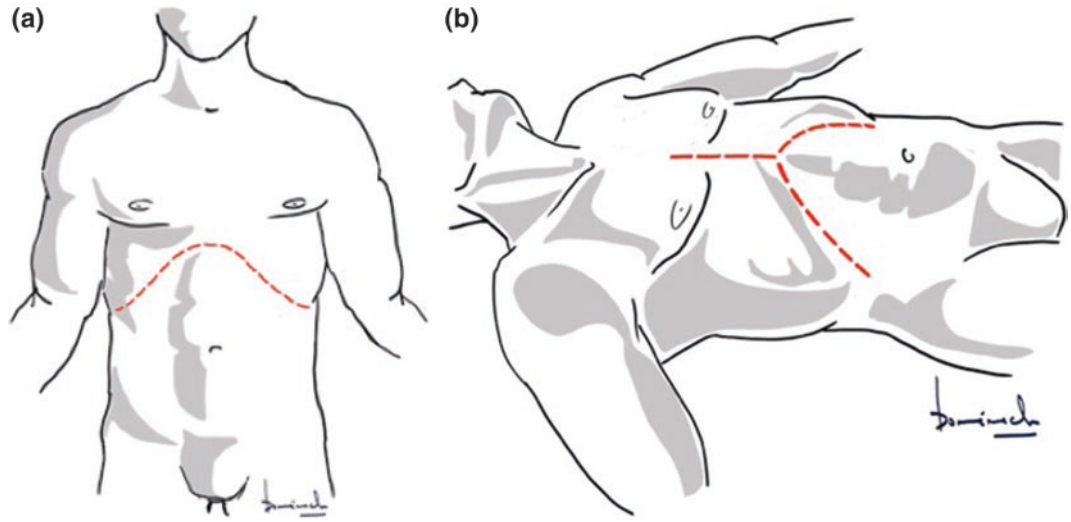

Fig. 10 Chevron incision consists of a bilateral subcostal access. If needed, it can be extended upwards with an additional cut on the midline, going beyond the xifoid

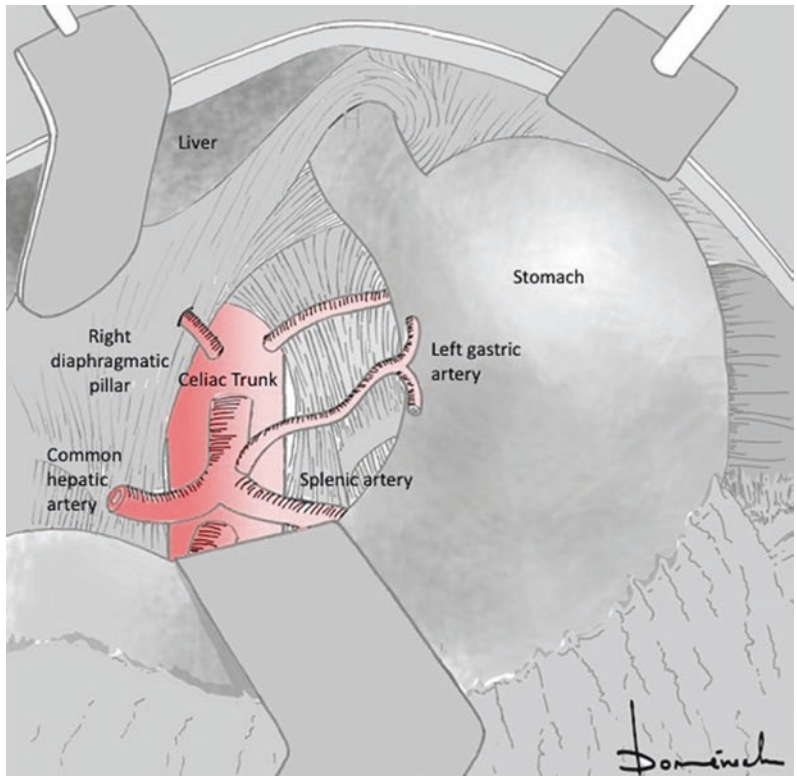

Fig. 11 Supramesocolic abdominal structures

partially opened in its central portion in order to provide access to the distal descending thoracic aorta.

Extended Incisions: Xifoidectomy, Partial Median Sternotomy

Median laparotomies can be easily extended upwards, performing a xifoidectomy or associating a partial median sternotomy (to reach the 4th intercostal space) (Fig. 12).

Access can be optimized after left retro-colic and retro-renal mobilization.

It allows accessing the distal, extra-pericardic, descending thoracic aorta without displacing the pericardium or the pleura, as well as accessing the intra-pericardic inferior vena cava. It allows cardiopulmonary bypass. It can be useful when there is the necessity of repairing traumatic vascular lesions (Fig. 13).

This approach will be discussed further in the "supra-mesocolic approach for the supra-celiac aorta" section.

Transverse Laparotomy or Horizontal Transperitoneal Approach

The patient is placed in supine position with the arms extended, with the cylindric inflatable pillow placed below the angles of the scapulae, or the operating table can be split to form a 20°–30° angle midway between umbilicus and xifoid.

A transverse median incision 2–3 cm long is made above the umbilicus. It is extended to reach 2 cm more lateral to the eternal border of the rectus muscle. A simultaneous incision of subcutaneous tissue and anterior aponeurosis of the muscle is performed. The anterior fascia of the rectum is incised transversally and the

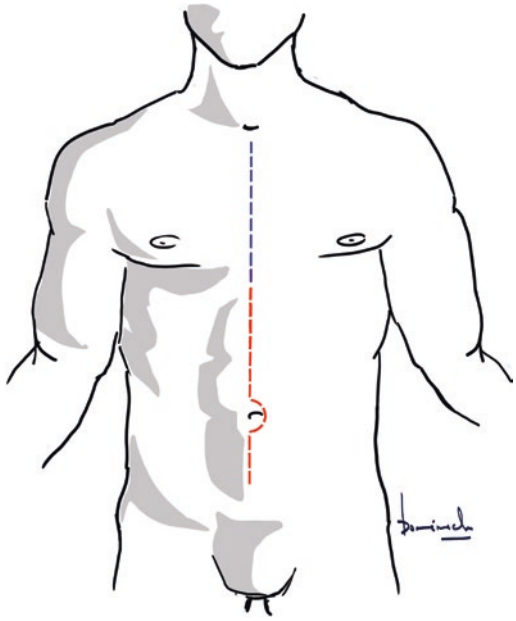

Fig. 12 Median laparotomies can be easily extended upwards, performing a xifoidectomy or associating a partial median sternotomy

incision is extended laterally to reach the anterior side of the aponeurosis of the major oblique muscle, in the same direction of its fibres.

After sectioning the aponeurosis, the rectus is freed and sectioned transversally with electrocautery, perpendicular to the direction of its fibres, after freeing its posterior adhesions.

This dissection requires meticulous control of haemostasis of the vascular pedicles, some of which will need to be ligated. Once this step has been completed, the posterior fascia of the rectus muscle, which is attached to the peritoneum, is incised.

The two borders of the incision are lifted up with the fingers in order to separate the wall from the underlying viscera. The peritoneum is opened on the median line and the opening is completed laterally.

This approach is usually performed without the need of intestine exteriorization. The greater omentum, the transverse colon and mesocolon are displaced upwards, down to the chest. The

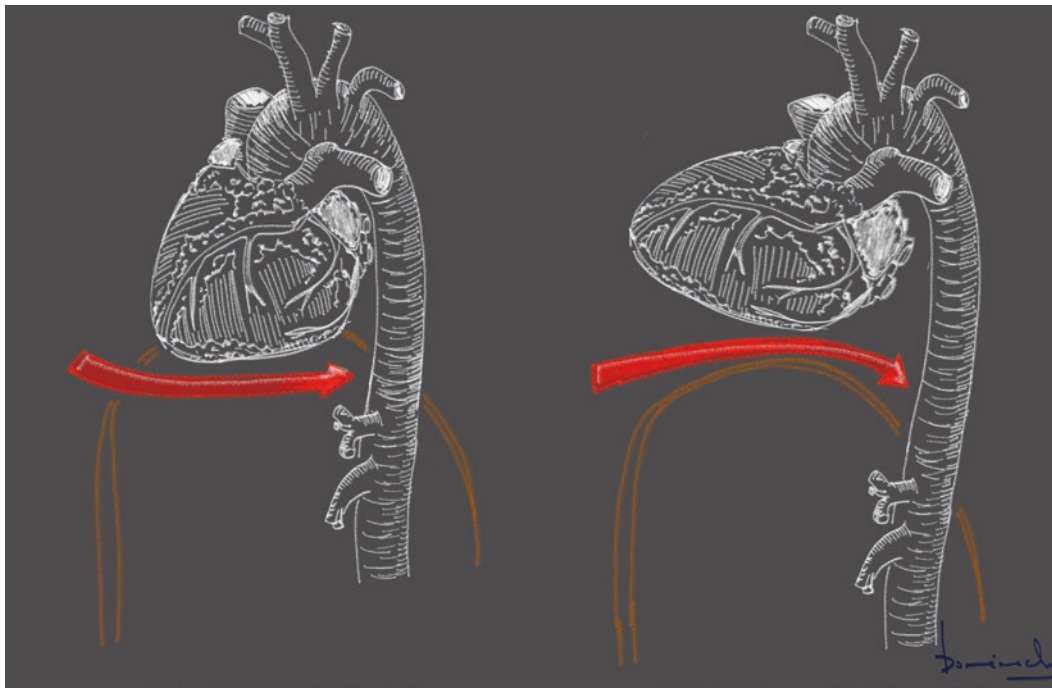

Fig. 13 Descending thoracic aortic approach: transperitoneum or intrapericardic access

small bowel loops are separated with three different packs, respectively: upwards and toward the right site, laterally towards the right parietocolic space, and downwards to the right. The sigmoid colon is displaced downwards and toward the left side. All viscera must be covered and protected with warm wet packs (Fig. 14).

If a multi-valve retractor is used, two valves are placed in the upper board to lift up the pancreatic-duodenal bloc. Another flexible valve is placed on the right side of the incision in order to keep the bowel loops in site. Another valve is placed inferiorly to displace bladder and sigmoid colon.

Exposure of the aorta is performed as described in the "longitudinal infra-mesocolic access" section.

☑ Sometimes, skin incision can be extended more laterally than the lateral border of the rectus abdominis muscles, so that it helps exposing the aorta in obese patients or if a simultaneous renal revascularization is planned.

Skin incision can also be performed in the shape of an arc, with the curve directed upwards, in order to improve exposure of the iliac vessels more distal to their bifurcation. The incision runs 2–3 cm below the umbilicus and is directed higher laterally to reach the external border of the rectus abdominis muscles, approximately 1–2 cm higher than the umbilicus.

The superior abdominal wall is lifted by means of a transfixed stitch at the epigastrium.

If there is the need of eviscerate the bowel loops after complete exposure has been completed, this can be performed in the same way as with a median laparotomy, but in this case this very approach would lose its advantages.

Transverse laparotomy without evisceration is considered less traumatic for the biomechanical characteristics of the abdominal wall (explained by the lines of tension of the abdominal wall).

☑ This approach is associated with les postoperative complications, lower postoperative pain, lower rates of postoperative ileus and hernia.

☒ On the contrary, this approach only exposes satisfactorily the infra-renal aorta. The exposure of renal arteries is limited and can be not appropriate to treat ostial lesions. Similarly, exposure of the iliac vessels is limited, but can be

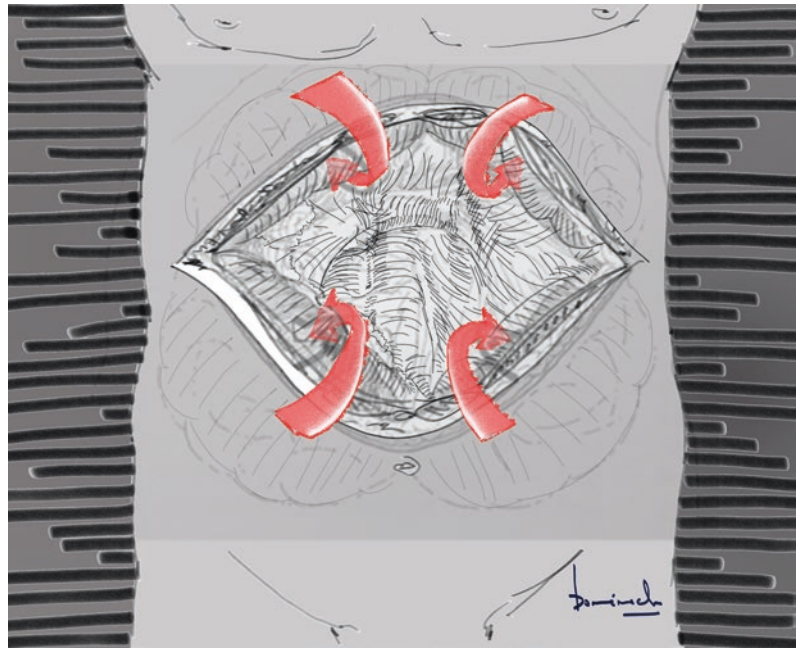

Fig. 14 Horizontal transperitoneal approach. All viscera are covered and protected with warm wet packs

improved with an arcuate incision (which can still be problematic). Lastly, extension upwards can be very limited and extremely difficult.

Manoeuvres

Longitudinal Inframesocolic Access

Adequate exposure of the aorta is essential to achieve safe and appropriate surgery. After median laparotomy and access to the peritoneum, the initial step to perform a correct exposition is represented by the upwards traction of transverse colon and greater omentum. This manoeuvre exposes the small bowel from the distal duodenum to the ileocecal junction.

A lateral traction toward the right side of the intestine allows the identification of the mesenteric root and of the ligament of Treitz.

If the small bowel needs to be eviscerated, the transverse colon is lifted up and covered with warm wet packs, placing a retractor to gently displace the bowel to improve visibility.

☑ Attention must be paid when eviscerating the bowel in order to avoid haemodynamic instability due to the manipulation of autonomic superior mesenteric nervous plexus.

If the bowel is maintained in the abdominal cavity, the loops are placed down the chest and toward the right abdominal wall, covered with packs. Retractors can be placed with caution.

☒ It is important not to leave any bowel loop uncovered to avoid lesions to the intestinal wall.

☑ Avoiding evisceration reduces the risk of postoperative ileus.

Posteriorly, retraction of the sigmoid colon toward the pelvis clearly exposes the retroperitoneum covering the aorta.

Dissection starts by means of cautious separation of the duodenum from the tissue involving the nearby aorta. After mobilizing the duodeno-jejunal angle, the Treitz is freed, allowing the mobilization of the 4th portion of the duodenum toward the right and to displace the duodeno-pancreatic bloc upwards (Fig. 15).

☑ Cautious manipulation during this step avoids lesions to the duodenal wall that can generate severe complications.

After mobilizing the duodenum, the incision of the retroperitoneum anterior to the aorta allows exposure of the anterior aortic wall (Fig. 16).

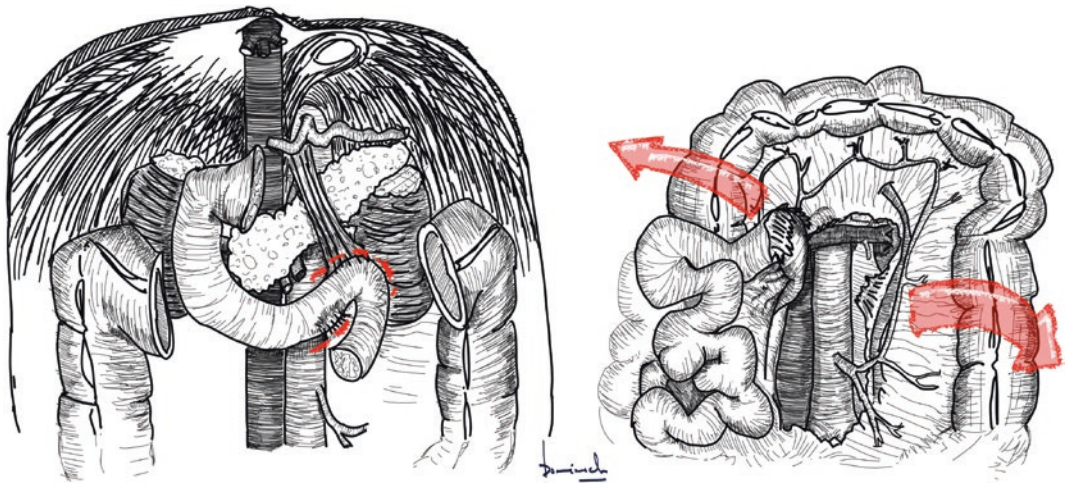

Fig. 15 Longitudinal inframesocolic access. Retroperitoneum covering the aorta is opened and the Treitz is freed, allowing the mobilization of the 4th portion of the duodenum toward the right and to displace the duodeno-pancreatic bloc upwards

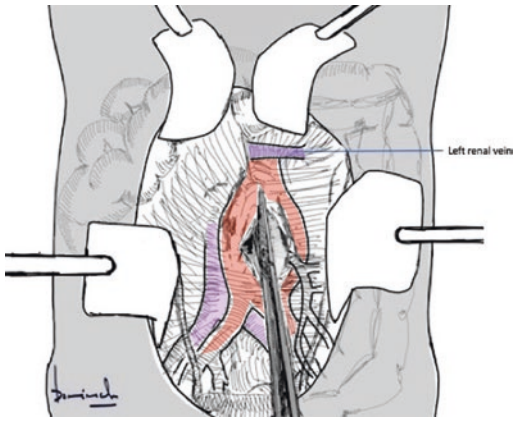

Fig. 16 Infrarenal aortic aneursym opened

☑ It is useful to leave an adequate margin of the retroperitoneum contacting with the duodenum in order to facilitate its closure once the procedure has been completed, taking into account the marked retraction which can later occur.

Valves of the retractor must be correctly placed so that a valve separates the left abdominal wall, another flexible valve gently displaces the small bowel to the right, and two more valves at the upper border of the peritoneal incision confer the shape of a "V" to the incision. Another retractor is cautiously used for the duodeno-pancreatic bloc (displacing it upwards and towards the right) and another lifts the peritoneal fold, exposing the IMV (Fig. 17).

☑ Depending on the extension of the incision or need to improve exposure upwards, IMV can be ligated and sectioned with no consequences.

The step allows to identify the left renal vein (LRV), which marks the upper limit of the aortic dissection.

The extension of the retroperitoneal incision cranially towards the proximal neck of the aneurism allows identification of the LRV.

☑ Cautious dissection of the LRV is crucial to avoid a venous lesion. It is seldom necessary to section the LRV to expose the proximal infra-renal aorta.

☒ Rarely, the LRV can be located behind the aorta, so it is important to know the anatomy of the patient preoperatively, by means of CT-angiography, in order to avoid

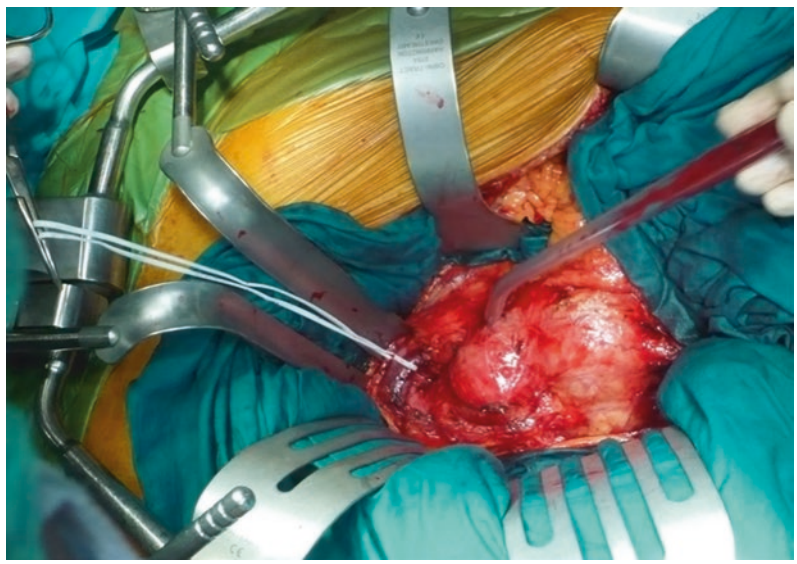

Fig. 17 Real case. Valves of the retractor must be correctly placed to infrarenal aortic aneursym exposure. Left renal vein is referenced using white seton

life-threatening venous damages (the renal blood flow is 1200 ml/min) during the proximal clamping.

Distal exposure of the abdominal aorta is achieved by extending the retroperitoneal incision caudally along the right anterior surface of the aneurism. The IMA is usually identified on the left anterior surface of the aneurism.

☑ Attention must be paid not to damage the IMA when opening the aneurism sac. It is known, however, that the IMA is chronically obstructed in most abdominal aorta aneurisms.

Depending on the distal extension of the aneurism, it might be necessary to prolongate the retroperitoneal incision down, lower than the iliac vessels.

☑ Autonomic nerves responsible of sexual function in men are usually located on the left common iliac artery, so this area should be avoided.

It is important to provide the patients with adequate information concerning the risk of postoperative sexual dysfunction because the anatomical variations of the nervous plexuses make sometimes impossible to avoid damaging them. Preservation of sexual function is favoured by limiting exposure of the aorta to the segment between the origin of renal arteries and the IMA, or by means of the retroperitoneal approach when the origin of iliac arteries is not manipulated.

☑ If the aneurism reaches below the left common iliac artery, some authors recommend a second retroperitoneal incision lateral to the sigmoid mesocolon, in order to gain access to the left iliac bifurcation.

Once the retroperitoneum that envelope the aorta has been completely opened, attention is moved to dissection of the aortic neck to achieve proximal control.

The LRV is gently mobilized and referenced with a vessel loop in order to achieve exposure of the proximal infra-renal aorta.

It is sometimes necessary to divide the LRV, hence several anatomical considerations must be taken into account.

Three important venous structures exist (adrenal vein, lumbar vein and gonadal vein) which would be left as the only venous drainage system for left kidney if the LRV is divided and not reconstructed (Fig. 18).

☑ Section of the LRV must be performed as much close to the vena cava as possible in order to preserve the above reported vessels and the venous return of the left kidney.

On the other hand, if division of the LRV is not required, these three veins can be sacrificed to achieve better mobilization of the LRV.

After adequate mobilization of the LRV, the dissection of the proximal neck of the aneurism is limited to the lax tissue associated with it.

In order to perform division with subsequent reconstruction of the LRV, it is recommended to create two purse strings close to the confluence of the vein into the vena cava. After division of the vessel, the purse string sutures are kept approximated with tourniquets so that haemostasis is maintained while the extremes are separated to expose the inter-renal aorta. Later the two ends of the vein can be sutured back together, once aortic reconstruction has been completed.

A systematic dissection of the aorta helps reducing inadvertent lesions of the lumbar arteries that originates from the posterior aorta.

☒ A circumferential dissection of the aorta is rarely required and is associated with higher risk of damaging the lumbar arteries.

Sometimes, wide lymphatic ducts are observed, which cross the aortic neck.

☑ Ligation of these lymphatic vessels reduces postoperative lymph leak.

The identification of renal arteries at this level can guide decision on the height of proximal clamping.

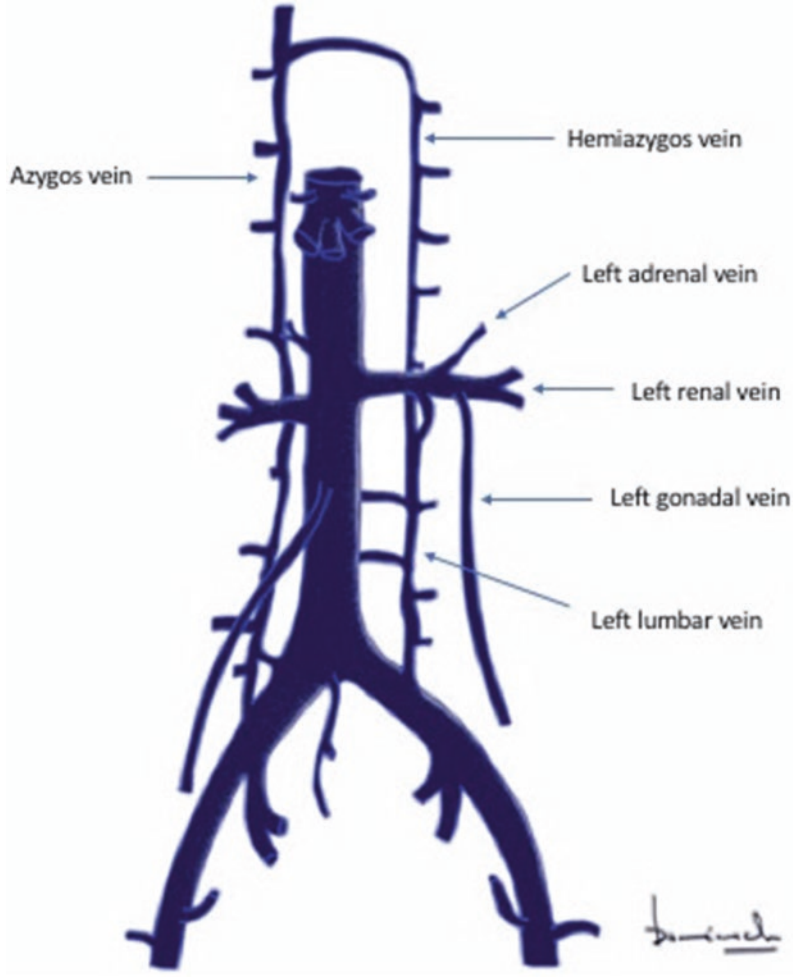

Fig. 18 Retroperitoneal venous structures which conform a venous drainage system

☑ Usually, a 1 cm margin of "healthy" infrarenal aorta is required in order to avoid a supra-renal clamping.

This margin allows to obtain adequate room for the clamping, leaving enough cuff to complete proximal anastomosis.

Attention must be paid to the vena cava, while dissecting the aorta. The cava is closer to the distal aorta and start gradually separating from it as it moves upwards.

An exception to what has been described in order to achieve proximal control is represented by a ruptured aneurism of abdominal aorta (AAA), especially if rupture occurred on the anterior face of the aneurism. Sometimes the haematoma generates the dissection itself, making the proximal control relatively easy, but it can be difficult in several cases.

☑ Ruptured AAA require immediate proximal control as soon as the peritoneal cavity is opened, at the level of supra-celiac aorta (described in the next section).

The precise location of the distal control site variates according to the extension of the aneurism or to occlusive disease. If the aneurism is limited to the aorta, control at the level of common iliac arteries will be sufficient.

A cautious dissection and a deep anatomical knowledge of the relations between iliac arteries and veins are required to avoid venous damages. Ilio-caval confluence is adhered to the aortic bifurcation.

Venous bleeding in the pelvis can be conspicuous, difficult to control, and life-threatening.

☒ Similarly to the proximal aorta, circumferential dissection of the iliac arteries is not usually required and increases the risk of the subjacent iliac veins.

Anatomy of the ureters must be known.

Before descending into the pelvis, the ureters cross bilaterally the distal common iliac arteries, cranial to their bifurcation.

☒ Attention must be paid not to damage the ureter when dissecting the iliac bifurcation.

Manipulation of ureters must be kept to the minimum and be performed with extreme caution to avoid damaging their fragile vascularization.

If the aneurism involves the common iliac arteries, distal control is achieved normally more distal to the iliac bifurcation. This means dissecting the external and internal iliac arteries, hence a wide mobilization of the sigmoid is required (Fig. 19). Under these circumstances, the distal anastomosis is usually made at the level of iliac bifurcation.

In the unlucky event of internal iliac aneurisms, distal control can be difficult.

☑ Endoclamp techniques by means of endoluminal occlusive catheters can be useful in case of aneurisms of the hypogastric artery, either to obstruct the aneurisms and to re-establish the pelvic blood flow.

Re-establishing the pelvic blood flow can be achieved by creating a lateral branch originating from the iliac branch of the bifurcated aortic insert.

☒ Independently from the level of distal control, it is important to avoid damaging the iliac veins. Lesions could lead to haemorrhagic shock and death.

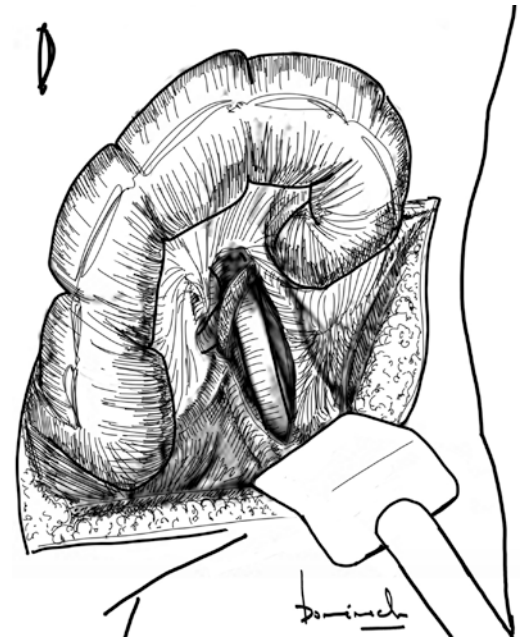

Fig. 19 Intersigmoid fossa showed after sigmoid mobilization. The ureter and left external iliac artery are the most frequently encountered structures during the dissection of the fundus of the intersigmoid fossa

Supramesocolic Access

Supraceliac Clamping

Difficulties in approaching the celiac aorta are marked between the thoracic aorta and the infra-renal abdominal aorta. This anatomic region is deep and difficult to access. This can be obtained either trans-peritoneally by means of visceral rotation or retro-peritoneally.

The patient is placed in supine position with a cylindric inflatable pillow located at the level of T12 to elevate the backbone.

After median laparotomy, the round ligament and the falciform ligament are divided, and a subcostal retractor is placed.

The left hepatic lobe (LHL) is mobilized by sectioning the triangular ligament and the hepatic coronary ligament, without reaching to the left supra-hepatic vein. The LHL is displaced toward the right and maintained in site by means of a valve.

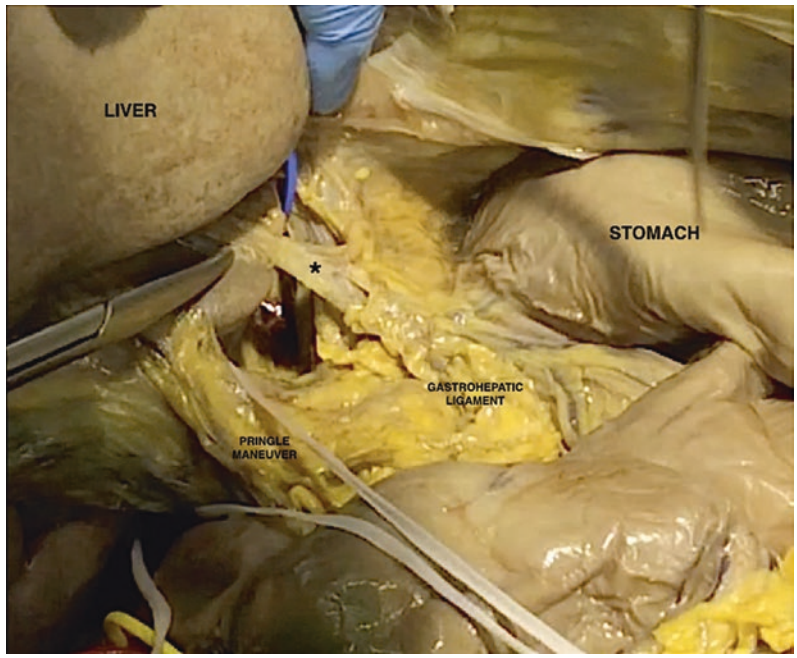

Fig. 20 Cadaveric dissection. Asterisk shows a left hepatic artery originating from left gastric artery

☒ A left hepatic artery can be found (asterisk in Fig. 20). If divided, postoperative ischemia and liver failure can occur.

After ascertain the absence of a left hepatic artery originating from the left gastric artery, the lesser sac is opened in its *pars flaccida*. Opening the epiploic cavity at this level gives access to the celiac region (Fig. 21).

The oesophagus is identified more easily if a nasogastric tube has been placed, and both vagus nerves are moved towards the left side. By pulling the stomach downwards, the arcuate ligament is identified. The latter is sectioned after placing a retractor to protect the celiac trunk and the aorta. The aorta is exposed sectioning the right diaphragmatic pillar (Fig. 22).

Frequently, the right diaphragmatic pillar is constituted by two stratus, one more superficial, made by principal fibres, and another which is deeper and formed by crossing fibres covering the aorta. The superficial portion is freed by dividing the median arcuate ligament, which attaches it to the left diaphragmatic pillar. The deeper segment is sectioned with electrocautery.

Then, the anterior surface of the aorta is freed for a total of 8–10 cm. Once exposed, the left and right phrenic arteries are ligated and divided. During these phases, the supra-celiac aorta can already be clamped.

☑ In ruptured AAA, infra-renal clamping can be very difficult. After opening the peritoneal cavity, manual palpation at the level of the diaphragmatic hiatus allows identification of the supra-celiac aorta and offers the opportunity of achieving rapid proximal control at this level.

The right pleural *cul-de-sac* is displaced upwards to obtain access to the supra-celiac aorta.

☑ For a bypass from the celiac aorta, the tunnel for the bypass and for the epiploplasty (if needed) should be prepared before aortic clamping.

For the tunnelization of such bypasses, the anterior surface of the transverse mesocolon is lifted and a tunnel is created through the basis of the

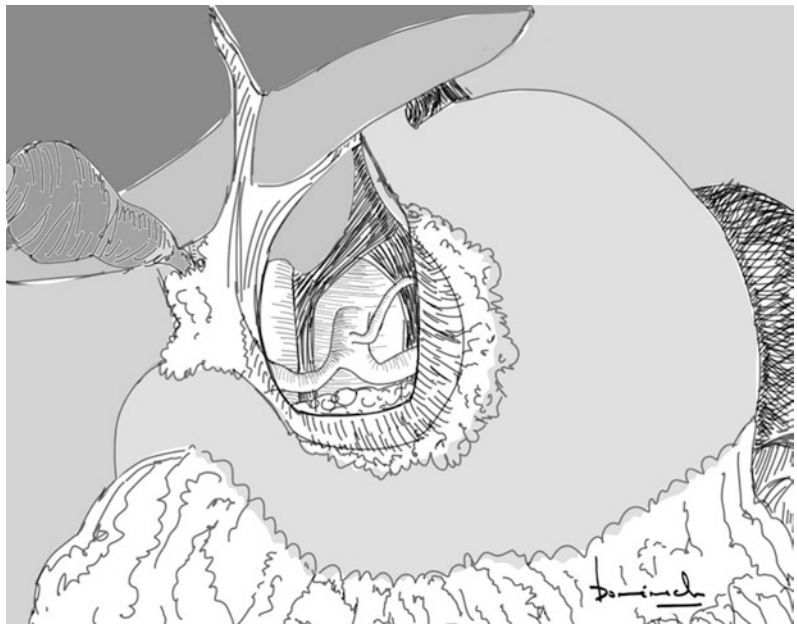

Fig. 21 Celiac region access after lesser sac is opened in its pars flaccida

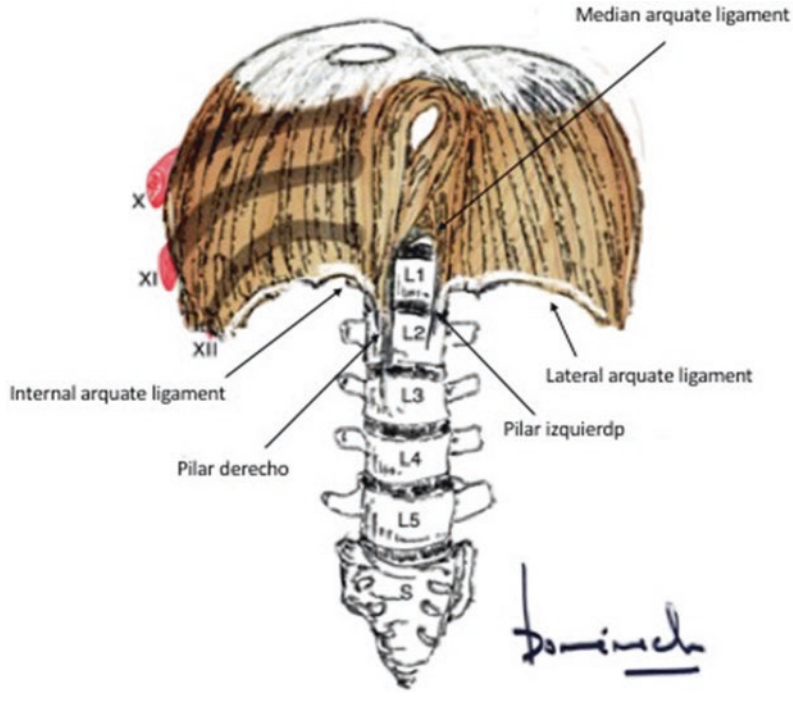

Fig. 22 Diagphragmatic attachment points

transverse mesocolon going to the left of the middle colic.

Three possible complications can occur with this approach.

☒ Risk of opening the pleura in the posterior infra-mediastinal region, minor problem that can be managed with a pleural drain.
☒ Risk of postoperative pancreatitis.
☒ Risk of gastroesophageal reflux after dividing the right crus of diaphragm, in patients with pre-existing anomalies of the oesophageal portion of the cardias.

This intraperitoneal approach can be uncomfortable due to its narrowness and deepness.

☒ This approach should be avoided in obese patients with a narrow thorax. However, it can be extended to perform a partial median sternotomy.

On the other hand, aortic clamping can be impossible in the event of atherosclerosis and severe calcification of juxta-renal aorta.

☑ It allows to clamp the supra-celiac aorta to repair juxta-renal aneurisms, which is preferred to supra-renal clamping in close proximity to the aneurism.
☑ It allows to revascularize the hepatic artery, the SMA, the renal arteries, or the femoral arteries from the celiac aorta.

Lastly, it is useful to remember the severe haemodynamic changes caused by clamping the aorta at this level, hence attention must be paid to monitoring and the anaesthesiologist should be made aware before removing the supra-celiac clamp.

☑ Slow removal of the supra-celiac aortic clamp helps preventing abrupt fall of arterial pressure.

Medial Visceral Rotation

Left (Mattox Manoeuvre): Retrorenal and Prerenal

The approach consisting of median laparotomy with medial and left visceral rotation was described by Mattox and popularized by Stoney, and represented a milestone in treating the supra-renal aorta. After median xifopubic laparotomy and placement of retractors, the procedures starts by dividing the triangular ligament in order to free and displace toward the right side the LHL. Then, the left parietocolic ligament is sectioned from its sigmoid parietal attachment to the phrenocolic ligament, and then the splenic flexure is mobilized together with the omental sac and the spleen, after sectioning it adhesions to the diaphragm (Fig. 23).

Medial rotation of the spleen eases mobilization of the splenic hilum and tail of the pancreas.

☒ Freeing the splenic adhesions and mobilizing the spleen represents the most delicate step of this approach due to the risk of rupturing the splenic capsule, which might require urgent splenectomy.

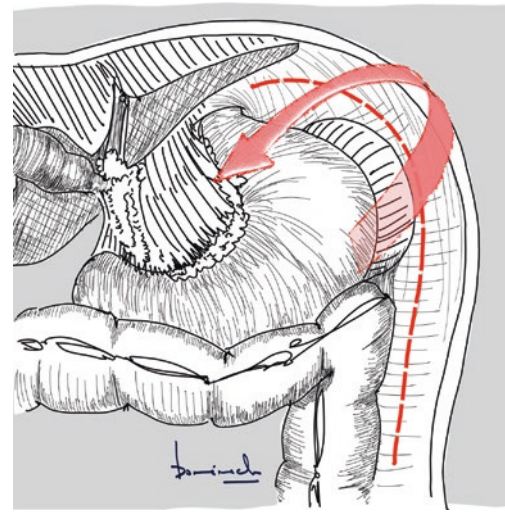

Fig. 23 Mattox manoeuvre

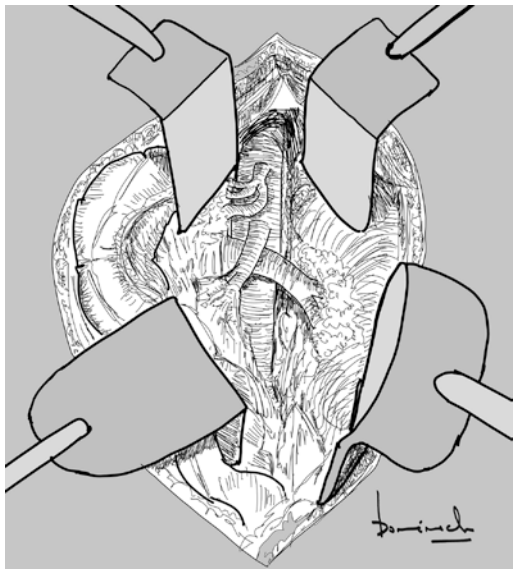

Fig. 24 Mattox manoeuvre. Prerenal approach

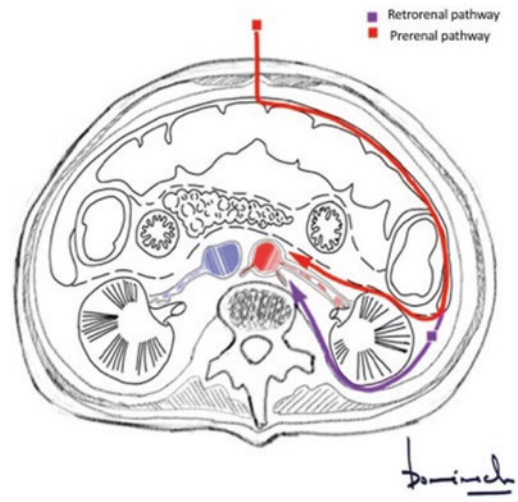

Fig. 25 Mattox manoeuvre. Prerenal and retrorenal approach

Then, the spleen and the tail of the pancreas, the stomach, and the left colon are displaced to the right and maintained in site with retractors. Therefore, only the kidney, the ureter, the adrenal gland, and the LRV draining into the vena cava are left in the posterior aspect of the dissection (Fig. 24).

Two possible strategies exist to approach the left kidney; it can be detached and retracted ventrally and to the right together with the other viscera (RETRORENAL APPROACH), or it can be left in situ in the lumbar region (PRERENAL APPROACH or MODIFIED MATTOX MANOEUVER) (Fig. 25).

☑ Retrorenal approach allows better access to the posterolateral surface of the aorta and to the left renal artery, and it is used primarily to access the supra-renal aorta.
☑ Prerenal approach allows exposition of the major segment of the SMA.
☒ In this case, attention must be paid when separating the kidney and the adrenal gland from the pancreas to avoid damaging these structures.

The left diaphragmatic pillar obstruct access to the aorta at the site where it goes through the diaphragm. Hence it can be sectioned or simply disconnected from the aorta after dividing the arcuate ligament. Sometimes it might be necessary to ligate and divide a diaphragmatic artery. The left celiac ganglion that covers the origin of the celiac trunk is sectioned, and the celiac trunk is identified close to the aorta. The SMA is exposed and controlled 1 cm below. It can be freed 4–6 cm distally to its origin.

The left renal artery is easily identified, either with the kidney rotated medially or with the kidney in situ.

The origin of the right renal artery and the perimeter of the infra-renal aorta can be referenced with vessel loops Dissection can be continued to the aortic bifurcation if required.

Median laparotomy with left medial rotation confers some advantages.

☑ It allows the same exposure of the aorta and of its branches than a thoracic-phrenic-lumbotomy, with lower morbidity.
☑ It can be adapted for anterograde revascularization and endarterectomies.
☑ It is suitable for concomitant renal and aortic surgery.
☒ Stoney described postoperative pancreatitis, which should be reduced during retrorenal

approach by avoiding excessive pancreas manipulation.

Another option is to carry out a MEDIAN LAPAROTOMY WITH MEDIAL VISCERAL ROTATION ASSOCIATED WITH A PARTIAL MEDIAN STERNOTOMY (described by Shirkey in 1967, popularized by Stoney, and later described by Blaisdell for the treatment of traumatic lesions of the superior abdominal aorta and of visceral arteries). This approach involves a xifopubic incision on the midline prolonged with a median, inferior, partial sternotomy. The patient is placed in supine position with the pillow below the basis of the thorax. The small bowel is displaced to the right and protected with warm wet packs. The left colon is mobilized by dividing the parietocolic ligament starting from the sigmoid colon upwards. The phrenocolic ligament is sectioned, and the spleen an tail of pancreas are mobilized to the right (Fig. 26). The dissection plane is defined by the pancreas (anteriorly) and the pre-renal fascia (posteriorly). In order to achieve a wider access to the celiac aorta, a retrorenal access can be used (Fig. 27). The latter allows a complete access to the juxta-renal, supra-renal, and celiac aorta (Fig. 28).

☑ If the prerenal approach is used and there are difficulties to find the planes (e.g. obese patients), the left ureter can be used as a landmark to be followed caudal-cranially.

The ureter is easily identified in the lower part of the incision, after mobilizing the sigmoid colon. Dissection is continued anterior to the left ureter, on the anterior surface of the aorta until reaching the LRV. The plane is easily extended anterior to the left kidney, until meeting the plane created during mobilization of the spleen and pancreas. Dissection is continued towards the right, rotating the stomach and subsequently dividing the triangular ligament of the liver, in order to rotate the LHL toward the right. This manoeuvre allows a complete exposure of the entire abdominal aorta.

The arcuate ligament and the diaphragmatic pillar are sectioned to access the supra-celiac aorta and open the infra-mediastinal space (Fig. 29).

In case of a MEDIAL INFERIOR PARTIAL STERNOTOMY, the lower portion of the descending thoracic aorta can be accessed by means of an extra-pericardic approach, after sectioning the phrenic centre and retracting the pericardium upwards.

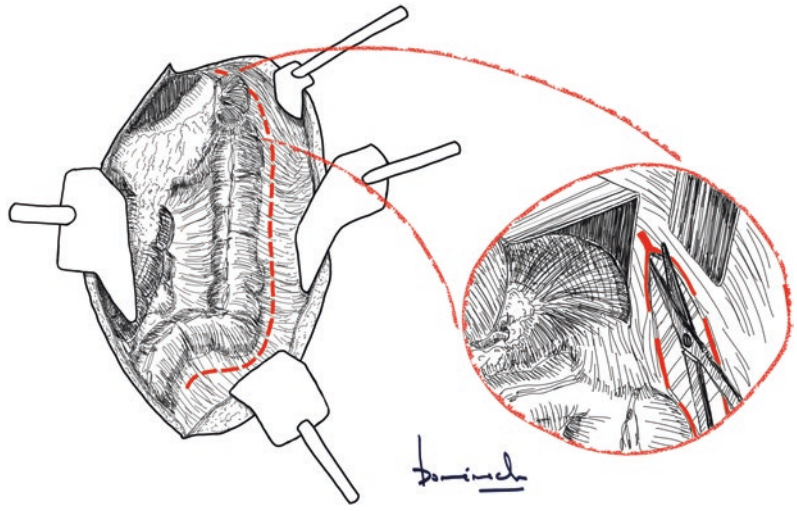

Fig. 26 Mattox manoeuvre. The left parietocolic ligament and phrenocolic ligament are sectioned and the spleen an tail of pancreas are mobilized to the right

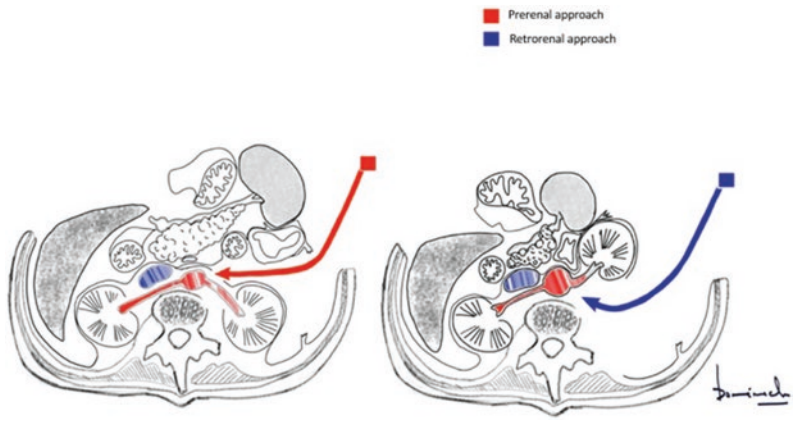

Fig. 27 Mattox manoeuvre. Prerenal and retrorenal approach

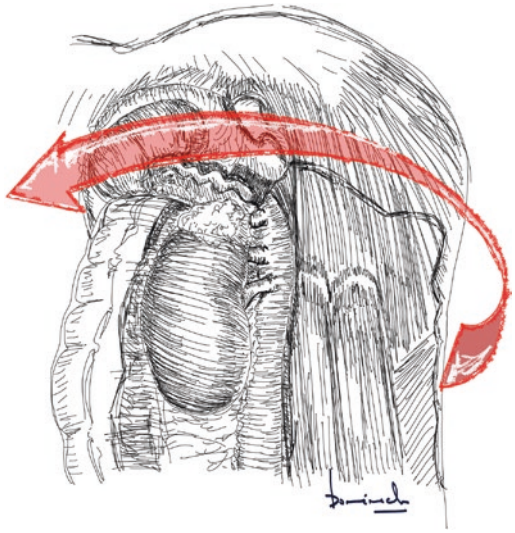

Fig. 28 Mattox manoevre retrorenal approach allows a complete access to the juxta-renal, supra-renal, and celiac aorta

Fig. 29 The arcuate ligament and the diaphragmatic pillar can be sectioned to access the supraceliac aorta

☑ An advantage of this approach is the possibility of achieving a wide access in a supine position, from the celiac aorta to the iliac vessels, including the femoral arteries.

☑ It is the approach of choice in case of emergent treatment traumas of the supra-renal abdominal aorta.

☑ It is also used during supra-renal transaortic endarterectomies used to treat occlusive lesions to CT and SMA.

☒ However, dissection is wider, and in heparinized patients it can cause significant intraoperative blood loss.

☒ It brings about a significant risk of splenic injuries (up to 21% in some series).

☒ There is the risk of acute pancreatitis with severe consequences (up to 5%).

Right (Cattell Braasch Manoeuvre). Kocher Manoeuvre

It involves medial rotation of all intra- and retro-peritoneal organs of the right side of the abdomen via a median laparotomy. It includes mobilization of the caecum, ascending colon, hepatic flexure through the white line of Toldt

(fascia originating from the embryologic coalescence of visceral peritoneum of the right colon and mesocolon and the retroperitoneum), as well as mobilization of the small bowel mesentery. The right colon and its mesentery are displaced towards the right superior quadrant.

☑ The manoeuvre allows excellent exposure of the aortic bifurcation and of the vena cava, presacral artery, and gonadal vessels. Also, it achieves excellent exposure of right ureter and kidney.

After median laparotomy, this right latero-colic approach begins with incision of the posterior parietal peritoneum of the hepatic flexure of the colon and is continued on the paracolic gutter.

The ascending colon is freed starting from the caecum, and it is displaced to the left together with small bowel loops. Then, a retroduodenal-pancreatic mobilization is performed with Kocher's manoeuvre (described later). The inferior vena cava is approached at the level of the origin of the renal veins, behind the second duodenal portion (Fig. 30).

The following step consists of liberation and exposure of the entire anterior surface and of the right lateral border of the inferior vena cava, requiring ligation and division of some branches, including the right gonadal vein. The aorta is exposed below the LRV,

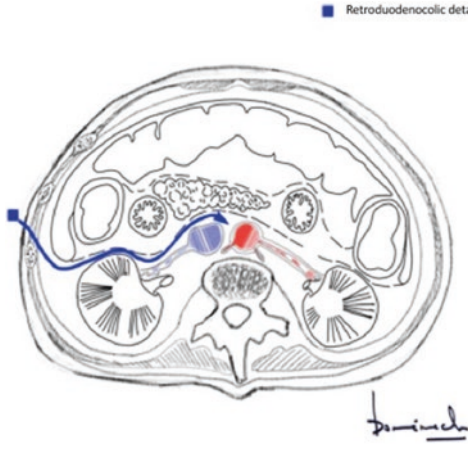

Fig. 30 Cattell Braasch manoeuvre

by dissecting its anterior wall on a cranial-caudal fashion. The infra-renal aorta can be exposed to reach its bifurcation, providing excellent exposure of inferior vena cava, caval-renal confluence, the right renal pedicle, the left kidney, and the right iliac artery (Figs. 31 and 32).

Kocher Manoeuvre:
It consists of dissection of the anterior plane of the vena cava, rotating medially the duodenum and the head of pancreas. The assistant surgeon must medialize the second portion of the duodenum with triangular forceps or with gentle hand traction, providing contra-traction with respect to the peritoneum. The operating surgeon combines blunt and sharp dissection to free the adherences of the duodenum and head of the pancreas to the retroperitoneum. This manoeuvre completes the Cattel-Brassch manoeuvre.

It helps exposing completely the vena cava, the posterior surface of the pancreas, and the second and third portions of the duodenum.

Combining both manoeuvres, it is also possible to achieve excellent exposure of the right kidney and of its vascular pedicle, as well as exposure of the aorta. Mobilization of the ligament of Treitz allows better exposure of the third and fourth portions of the duodenum.

Access to the infra-renal aorta is easy and the techniques described might not be necessary. However, the small benefit which can be obtained by adopting an approach that is unusual for a specific aim could contribute to the success of the procedure in selected cases. Cardiovascular surgeons should be aware and master of the different approaches and accesses available.

Summary

Access to the abdominal aorta by its different approaches and deep knowledge of anatomy should be controlled by all cardiovascular surgeons as every single case should be individualized to achieve success.

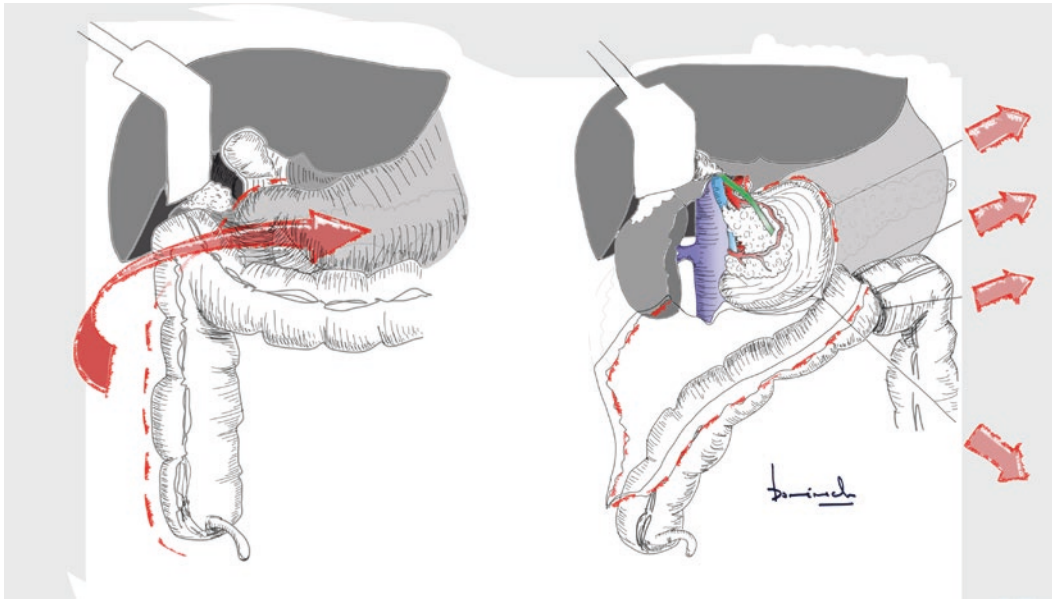

Fig. 31 Cattell Braasch manoeuvre. The right parietocolic ligament is sectionet and duodenum and the head of pancreas are medially rotated (Kocher Manoeuvre)

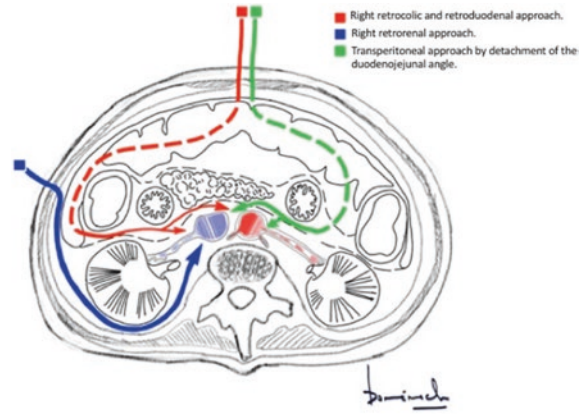

Fig. 32 Different routes to exposure right retroperitoneal structures

Self-study

1. **Which of the following sentences is false?**
   (a) Midline laparotomy is associated with relevant respiratory complications, with up to 50% reduction of vital capacity. CORRECT.
   (b) Chevron provides a good exposure of supra-mesocolic compartment and for medial visceral rotations. CORRECT.
   (c) Chevron is the preferred incision for vital emergencies. FALSE. Midline laparotomy is the approach of choice in emergencies because of its speed to be performed and the wide range of maneuvers it allows.
   (d) In ruptured abdominal aortic aneurysms on its anterior face it is strongly recommended to perform a direct supraceliac aortic clamping. CORRECT.

2. **Which of the following sentences is false?**
   (a) Attention must be paid not to divide a left hepatic artery during supraceliac aortic clamping. CORRECT.
   (b) A retro-aortic left renal vein can be found in a minority of patients. CORRECT.
   (c) There exists a risk of splenic injury and pancreatitis during Mattox maneuver. CORRECT.
   (d) Mattox maneuver allows a better exposure of vena cava than Cattell Braasch maneuver. FALSE. Cattell Braasch manoeuvre is the right visceral rotation and combined with Kocher manoeuvre allows excellent exposure of inferior vena cava and the cavo-renal confluence.

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Extended Criteria and Donation After Circulatory Determined Death (DCD) Donors for Lung Transplantation

James B. Barnard

Key Points

1. Extended criteria donor lungs constitute a significant proportion of organs utilised for lung transplantation.
2. Overriding a single factor from the standard donor lung acceptance criteria can often be justified based on the good outcomes of multiple reports.
3. Challenging decision-making arises when there is more than one area in which the donor is suboptimal and lung donor-scoring systems have been developed to help clinicians.
4. A combination of low-risk recipient and low-risk donor has the highest 1- and 5-year survival whereas a combination of high-risk recipient and high-risk donor has the lowest.
5. Donation after circulatory determined death (DCD) has increased from 0.6% in 2003 to 15.2% in 2017 in the international registry and has good outcomes.
6. It is preferable for donors who would fulfil brain death criteria to proceed as DBD rather than DCD since donor lung utilisation is significantly more likely from this technique.
7. Ex-Vivo Lung Perfusion (EVLP) is an accepted method to assess lungs using a rig that both ventilates and perfuses the lungs outside of the body to enable utilisation of extended criteria lungs.

The growing populations of patients with end-stage lung diseases for which lung transplantation (LTx) represents the only hope for improved quality of life and increased survival has fuelled the need to extend the boundaries of lung donation. In order to address the growing waiting times for LTx candidates and the high mortality on waiting lists, transplant teams need to utilise as many potential lung donors as possible. Donors outside of the originally proposed criteria [1] have been increasingly used [2–6]. In this chapter the potential benefits and risks of utilising extended criteria donors will be described together with the practice of donation after circulatory determined death (DCD). The use of ex-vivo lung perfusion (EVLP) techniques will also be briefly mentioned.

Extended Criteria Donors

Lung donors who fall outside of the original acceptance criteria suggested by Cooper et al. [1] may be considered extended criteria donors (ECD). However, there is no internationally agreed consensus on a precise definition. ECD

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lungs have long made up a significant proportion of organs utilised and account for between 40 and 50% of donor lungs transplanted in some programs [5, 7–9]. There are no standardised acceptance thresholds for many of the donor physiological parameters. Even some long held absolute contraindications such as hepatitis C infection in the donor are in the process of being revoked [10–12]. Organ acceptance criteria are continually revised and broadened in each transplant program according to experience and outcomes. The decision-making becomes more complex when more than one donor parameter falls outside of the acceptance threshold.

Age

Initial recommendations suggested that donors below the age of 50–55 years can be accepted [1, 2, 4]. This age limit has been relaxed [2] and donors aged into their seventies are accepted in some rare cases [13]. Reports of outcomes analysed purely based on the age of the donor suggest that there is limited impact on the short and medium term [14–16]. Outside of these clinical outcomes, however, there is physiological evidence that our lungs deteriorate into the sixth, seventh and eighth decade of our lives [17] and this may be detrimental to a recipient seeking long-term survival.

A United Network for Organ Sharing (UNOS) database analysis of 15,844 propensity matched LTx recipients stratified by donors younger or older than 60 years found no differences in survival. The report concluded that even though donor and recipient age may be important in LTx, the interplay between donor and recipient age alone is not an independent determinant of survival [14]. In a 128 patient study by Pilcher et al., higher donor age correlated with lower PaO_2/FiO_2 ratio in the early post-transplant period but again, there was no difference in long-term outcome [18]. However, another UNOS database study on 14,222 lung recipients transplanted between 2005 and 2014, stratified by recipient age 50 years or less, donor age 60 years or more, and single versus bilateral lung transplantation (BLT) showed that donor lungs aged 60 years or more was associated with slightly worse 5-year survival (44% vs. 52%; $p < 0.001$). Among recipients older than 50 years, this trend was not present in the multivariate model (hazard ratio 1.23, $p = 0.055$). Among recipients aged 50 years or more who received older donor lungs, survival was impaired in single lung transplantation (SLTx) but no significant difference was seen in survival following BLTx between those receiving younger and older donor lungs. This study concluded that reasonable post-transplant outcomes could be achieved with use of advanced age donors in all recipient groups and proposed that BLTx should be performed when older donor lungs (age more than 60) are used in younger recipients (age 50 or less) [15].

Smoking

Initial guidelines suggested that lung donors should be non-smokers [1]. With time and the growing population of recipients awaiting LTx, this restriction has been relaxed and a smoking history in lung donors is now widely accepted. Understandably there are concerns about using smokers' lungs. Attempts have been made to determine the risk of using lungs from donors with a significant smoking history versus the risk of dying on the waiting list whilst awaiting a LTx. Bonser et al. [19] examined the consequences of donor smoking on post-transplant survival, and the potential effect of not transplanting lungs from such donors on 3 year survival. In 1,295 LTx recipients, the 39% who received lungs from donors with positive smoking histories had worse 3-year survival than those who received lungs from donors with negative smoking histories (unadjusted hazard ratio [HR] 1.46, 95% CI 1.20–1.78; adjusted HR 1.36, 1.11–1.67). Independent factors affecting survival were recipient's age, donor-recipient cytomegalovirus matching, donor-recipient height difference, donor's sex, and total ischaemic time. Of 2,181 patients registered on the waiting list, 802 (37%) died or were removed from the list without receiving a transplant.

Patients receiving lungs from donors with positive smoking histories had a lower unadjusted hazard of death after registration than those who remained on the waiting list (0.79, 95% CI 0.70–0.91). Patients with septic or fibrotic lung disease registered between 1999 and 2003 had risk-adjusted hazards of 0.60 (95% CI 0.42–0.87) and 0.39 (0.28–0.55), respectively. The authors concluded that in the UK, an organ selection policy that uses lungs from donors with positive smoking histories improved overall survival of patients registered for LTx, and should be continued. Although lungs from such donors were associated with worse outcomes, the individual probability of survival was greater if the patient accepted these lungs rather than chose to wait for a transplant from a lung donor with a negative smoking history.

Smoking of Cannabis and Cocaine

Concerns about using lungs from donors who have smoked cannabis are based on the reported damage on the lungs including an increased risk of pneumothorax, bullous emphysema, lung hyperinflation and chronic obstructive pulmonary disease [20]. Cannabis use is common in the population (12.4 and 5.4% of 15–64 year olds in the United States and Europe respectively) [21]. The Harefield group have described outcomes of LTx utilizing lungs from donors with a history of cannabis smoking in 19 cases and have compared these with the outcomes of 283 with no such history. All the donors in the 'cannabis' group were tobacco smokers compared with 43% in the control group. The history of donor cannabis smoking did not appear to affect early and mid-term outcomes after LTx [22]. Alkaloidal cocaine (crack cocaine) smoking is associated with a number of acute pulmonary complications including acute lung injury [23] and acute respiratory symptoms [24]. A recent review of the literature regarding the effects of drug abuse and smoking concluded that there is no overall evidence of effects of cannabis or cocaine on survival after LTx but that in all cases careful donor assessment should establish if a particular organ can be used [25].

Suicidal Hanging Donors

Lung donors who have hung themselves are considered high-risk donors. Aganiadou et al. compared the outcomes of 22 recipients who received lungs from suicidal hanging donors with 243 controls. No difference in chronic allograft dysfunction-free survival was found between the two groups at 1 or 3 years. Cumulative survival rates were similar between the two groups 68.2 versus 83.2% at 1 year and 68.2% versus 72% at 3 years ($p = 0.38$). The authors recommended the consideration of lungs from hanging donors [26].

Donor Malignancy

The guidelines suggest that low grade skin cancers, carcincoma in-situ and certain tumours of the central nervous system should be acceptable in the donor (Table 1). A history of cancer of the lung, bowel, kidney and breast or malignant melanoma is unacceptable unless the cancer is proven to be cured and there has been a significant cancer-free time interval. Ison et al. [27] have reported donor derived transmission of malignancy in transplant recipients and resulting death attributable to donor derived malignancy. In a study of 145 donors with a history of a prior malignancy, there was confirmed transmission in 28 recipients with resultant death in 10. In this study, renal cell carcinoma was the commonest donor malignancy accounting for 64 of the 145 cases with 7 transmissions and 1 death. However, it is difficult to draw firm conclusions from the limited data available. To minimise the risk of transmission of malignancy, it is important to assess all available medical history, undertake a thorough assessment of the donor especially at the time of retrieval, and it may be necessary to arrange an emergency pathology assessment of any suspicious lesion found.

Table 1 Summary of literature for donors with a history of malignancy

Acceptable
Low grade skin cancer (basal cell and squamous cell)
Carcinoma in-situ of organs such as the uterine cervix
Primary tumours of the central nervous system
If there are risk factors for metastases consider organs as marginal including:
High-grade histology
Glioblastoma and meduloblastoma
Previous craniotomy
Ventricular shunts
Tumour radiation
Recurrent disease in the brain, or a long interval from primary therapy
Not acceptable (consider as marginal if previous treatment with presumed cure)
Renal cell cancer
Lung cancer
Melanoma
Choriocarcinoma
Breast cancer
Colon Cancer

Reproduced from Orens et al. Summary of literature for donors with a history of malignancy [66]

Arterial Blood Gases

The guidelines have suggested that a PaO_2 of >350 mmHg or >300 mmHg is necessary for a lung donor. However, an analysis of UNOS data including 12,545 SLTx and BLTx recipients showed that donor PaO_2 <300 mmHg (20% of donors) and <200 mmHg (15% of donors) had no effect on recipient survival. Furthermore a Cox's multivariate analysis of 21 donor characteristics demonstrated that donor PaO_2 had no impact on graft survival [28]. Donor pulmonary vein gases can provide further information to transplant teams, help localise lobar issues and determine the viability of separate lungs [29–31]. If a BLTx cannot proceed because one donor lung is deemed un-transplantable, the ability to correlate poor gas exchange with localised chest X-ray or intraoperative findings can potentially enable a SLTx to proceed if a suitable backup recipient had been identified at the outset. An initial poor arterial blood gas in isolation should not be a reason to decline a lung donor as ventilator recruitment manoeuvres, the use of positive end expiratory pressure together with bronchoscopy and suctioning of secretions from the airway may achieve significant improvements prior to retrieval.

Radiology

Imaging is important to help identify conditions in the donor that are associated with poor clinical outcome [32]. A chest X-ray is mandatory for all lung donors and is a reported reason for declining a potential donor in around 12% of cases [33]. The ability of a chest X-ray to rule in or out lung pathology in the donor is limited when compared to a CT thorax. Increased use of CT scanning in donors may reduce the number of donors accepted as conditions such as interstitial lung disease and emphysema, that were not previously picked up on a chest X-ray, are detectable [34]. However, with the challenges in organising a CT thorax for a donor, proceeding to direct surgical assessment of the donor lung is often preferred as it provides an opportunity to assess the overall quality of the lungs, inspect for bullous disease, palpate for occult nodules or consolidation, evaluate the ability to re-inflate atelectatic segments and perform a deflation test.

Infections

Lung donors should be assessed carefully to determine if they are carrying infectious agents that may detrimentally affect the transplant

outcome. History, examination and investigations will help to determine if any infectious agents are present and a risk to a potential recipient. Some donor bacterial infections such as tuberculosis, gangrenous bowel or meningitis are unacceptable. Active viraemia in the donor of Herpes simplex, Varicella zoster, or cytomegalovirus, together with HIV infection or reactive hepatitis B surface antigen are absolute contraindications. In terms of the extended criteria donors, there is a recent report of 36 Hepatitis C negative recipients receiving lungs from donors with Hepatitis C viraemia. With 4 weeks of antiviral treatment all patients were free of Hepatitis C at 6 months following their transplant [12] and there is also experimental evidence that Hepatitis C can also be cleared in EVLP models [11]. Cryptococcal, aspergillus and histoplasmosis fungal infections are contraindicated.

Extended Criteria Donors and Lung Donor Scoring Tools

Overriding a single factor from the standard donor lung acceptance criteria can be reasonably justified based on the good outcomes of multiple reports. The more challenging decision-making arises when there is more than one area in which the donor is suboptimal. To assist clinicians in determining which donors may be used and to help with an understanding of the potential impact, several lung donor-scoring systems have been developed [4, 35].

Smits et al. analysed 6,080 LTx from the Eurotransplant database performed between 1999 and 2007 to create a lung donor score. Based on observed discard rates and using multivariate regression, points were assigned for six donor variables which were found to significantly predict declining organs: age, compromised history, smoking, shadow on chest X-ray, purulent secretions on bronchoscopy, and PaO_2/FiO_2 ratio <300 mmHg. Non utilization rates for donors with a lung donor score of 6 points (class 1) was 18%, 7–8 points (class 2) was 36% and 9+ points (class 3) was 54% ($P < 0.001$). In addition, the lung donor score was significantly associated with 1-year survival: class 1: 91%; class 2: 80%; and class 3: 72% ($P = 0.017$). The lung donor score accurately reflected the likelihood of organ acceptance and predicted recipient survival, and its application at the time of donor offer may facilitate donor risk assessment and recipient selection [4].

Whited et al. used a Cox proportional hazard model analysis on 9,408 patients from the UNOS database to identify donor risk factors associated with post-transplant survival. Each significant donor risk factor was assigned a score based on its hazard ratio and a donor risk score was calculated by adding the individual donor risk factor scores so that multiple risk factors were accounted for. Donors were then categorized into low-risk (score = 0), intermediate-risk (score = 1), and high-risk (score > 1) categories. The Lung Allocation Score was used as a surrogate for recipient risk. The 1-year post-transplant recipient survivals were 85%, 81%, and 77% for low-, intermediate- and high-risk donors respectively; the respective 5-year survivals were 53%, 50%, and 42% ($p < 0.001$). The combination of low-risk recipients and low-risk donors had the highest 1- and 5-year survival of 89% and 59%, respectively. The combination of high-risk recipients and high-risk donors reduced the 1- and 5-year survival to 70% and 30%, respectively. This proposed lung donor scoring system is a simple method that can aid transplant surgeons in the selection of a potential lung donor and is able to take into account the impact of multiple risk factors. In conjunction with an understanding of recipient risk this scoring system can help to provide an objective guide to predict potential 1- and 5-year outcomes [36].

Donation After Circulatory Death

Donation after circulatory determined death (DCD) was the mode of organ donation for the first attempt at lung transplant [37]. With the gradual acceptance of the definition of brain death in the 1970s, DCD became superseded. However, subsequent donor organ shortages

Table 2 The modified Maastricht classification of DCD

Category I. Uncontrolled	*Found dead* IA. Out-of-hospital IB. In-hospital	*Sudden unexpected CA without any* attempt of resuscitation; *WIT to be considered according to National-recommendations*
Category II. Uncontrolled	*Witnessed cardiac arrest* IIA. Out-of- hospital IIB. In-hospital	Sudden unexpected irreversible CA with *unsuccessful resuscitation l*
III. Controlled	*Withdrawal of life-sustaining therapy*	Planned withdrawal of life-sustaining therapy; expected CA
Category IV. Uncontrolled Controlled	*Cardiac arrest while life-brain dead*	Sudden CA after brain death diagnosis during donor life-management but prior to planned organ recovery

CA circulatory arrest, WIT warm ischaemic time

[a]This category mainly refers to the decision to withdraw life sustaining therapies. Legislation in some countries allows euthanasia (medically assisted CA) and subsequent organ donation described as the fifth category [38]

mandated reconsideration of DCD organs in the 1990s. The first report of a successful human DCD LTx came from Steen et al. in 2001. DCD is categorized by the Maastricht classification [38] (Table 2). The report from Steen et al. was of an uncontrolled Maastricht category II DCD donor. Most DCD donation in the current era though is from category III controlled donors.

The retrieval of DCD lungs differs from that of DBD in that national and local legal and ethical considerations determine the assessment modalities that are permitted. The potential DCD donor may have had X-ray or CT scan images as part of their management prior to the decision to withdraw life sustaining therapy (WLST). There may be arterial blood gas analysis and other blood results. However, in some countries such as the United Kingdom, ante-mortum interventions on the patient prior to WLST (such as fibre optic bronchoscopy) is not permitted. Other useful assessments such as pulmonary venous blood gas analysis as used in DBD lung donors are also not available to help the transplant team determine the suitability of DCD lungs for transplant. Fibre optic bronchoscopy can only be performed after confirmation of death and reintubation of the donor. This has to be carried out in parallel with surgical exploration and visual/tactile assessment of the lungs.

Warm Ischaemic Time

Experimental data suggest that lung tissue can tolerate 60–90 minutes of warm ischemia after circulatory death [39, 40]. Once life-sustaining therapies have been withdrawn, a judgement needs to be made about the time point at which warm ischemia commences. The ISHLT DCD working group have suggested the following definitions for various time points for DCD donation [41]:

- T0 withdrawal of life-sustaining therapies (WLST)
- T1 oxygen saturation < 80%
- T2 systolic blood pressure < 50 mmHg
- T3 cessation of cardiac output/asystole
- T4 resumed lung inflation/ventilation
- T5 start of pulmonary flush.

The current acceptable warm ischaemic time for DCD lungs range between centres from 60 to 90 minutes. Of the potential DCD donors proceeding to WLST, 30–40% become asystolic within such periods [42]. Thereafter, there is an obligatory observation period before death is confirmed. This varies from 2 to 20 minutes depending on local and national regulations.

In order to minimise delays following asystole, the retrieval team members are usually

gowned/gloved and waiting in the operating room from the point of WLST. It is only after death has been confirmed that the retrieval teams are allowed to proceed with re-intubating the trachea and rapid midline sternotomy/laparotomy. As soon as the pericardium is opened, boluses of heparin and prostacyclin are injected into the pulmonary trunk. A rapid assessment of the DCD lungs is made with fibre-optic bronchoscopy and surgical inspection. If a decision is made to proceed with retrieval of the lungs, the preservation technique used is similar to that used for DBD lung retrieval. Retrograde flushing of the DCD lungs may have an important role to flush out any blood clots that may have formed within the pulmonary vasculature. To date, the majority of the DCD lungs that have been accepted were transplanted directly from cold storage. The use of EVLP to assess or recondition DCD lungs depends on the availability of this resource and also the experience of the implanting centre.

Ex-Vivo Lung Perfusion (EVLP)

In their report on lung donation after circulatory death, Steen et al. also reported on the use of ex-vivo assessment of the lungs using a rig that both ventilated and perfused the lungs outside of the body [43]. The aims of this technique were to provide an assessment tool and to potentially recondition suboptimal lungs, e.g. pulmonary oedema that may be improved by perfusion with high oncotic pressure fluids. Extensive laboratory work underpinned the feasibility of EVLP and the first human case in 2001 [44, 45]. Over subsequent years, teams from Lund [46, 47] and Toronto [48, 49] have developed different clinical approaches.

Techniques of Ex-Vivo Lung Perfusion

The Lund EVLP protocol uses a perfusate consisting of Steen solution (XVIVO Perfusion, Sweden) which is a buffered human serum albumin and dextran 40 solution with added packed red cells to deliver a haematocrit of 15%. The pulmonary artery is cannulated for perfusion; the left atrial cuff is left open and allowed to drain into a reservoir beneath the lungs before being re-circulated (Fig. 1). Perfusion is initiated at 100 ml/min and as the lungs are rewarmed, perfusion is gradually increased up to the calculated full cardiac output for the donor while maintaining the perfusion pressure <20 mmHg. When the temperature reaches 32 °C, ventilation is commenced with a minute volume of 1 L/min. This is increased by 1 L/min for every degree increase in temperature until full ventilation at 100 ml/kg/min is reached. A PEEP of 5 cm H_2O is used with a tidal volume of 7 ml/kg body weight at a rate of 20 breaths per minute. Bronchoscopy can be performed if necessary. EVLP is continued over a period of 4–6 hours. If the lungs fulfilled the assessment criteria, the perfusion is set to cool the lungs back to 4 °C at which temperature the lungs are preserved prior to implantation (Fig. 2a).

For the Toronto protocol, EVLP is performed with Steen solution (XVIVO Perfusion, Sweden) without added blood. The left atrium is connected to the circuit by a cannula so that the lungs are perfused through a closed circuit. Atrial and pulmonary artery pressures are monitored during the perfusion. Ventilation is started at 32 and at 37 °C the flow through the lung is brought up to a maximum of 40% of the donor predicted cardiac output [50]. Left atrial pressure is maintained in the range of 3–5 mmHg by adjusting the height of the reservoir and the mean pulmonary artery pressure is kept between 10 and 15 mmHg (Fig. 2b).

Organ Care System (OCS) for Lung

The OCS Lung (TransMedics, Andover, Massachusetts) is a portable device designed to perfuse the donor lungs immediately after procurement with the aim of reducing ischaemic time of the organs. It also allows ventilation of the lungs during normothermic machine perfusion (Fig. 2c). The OCS Lung is transported to the donor hospital and can continuously perfuse

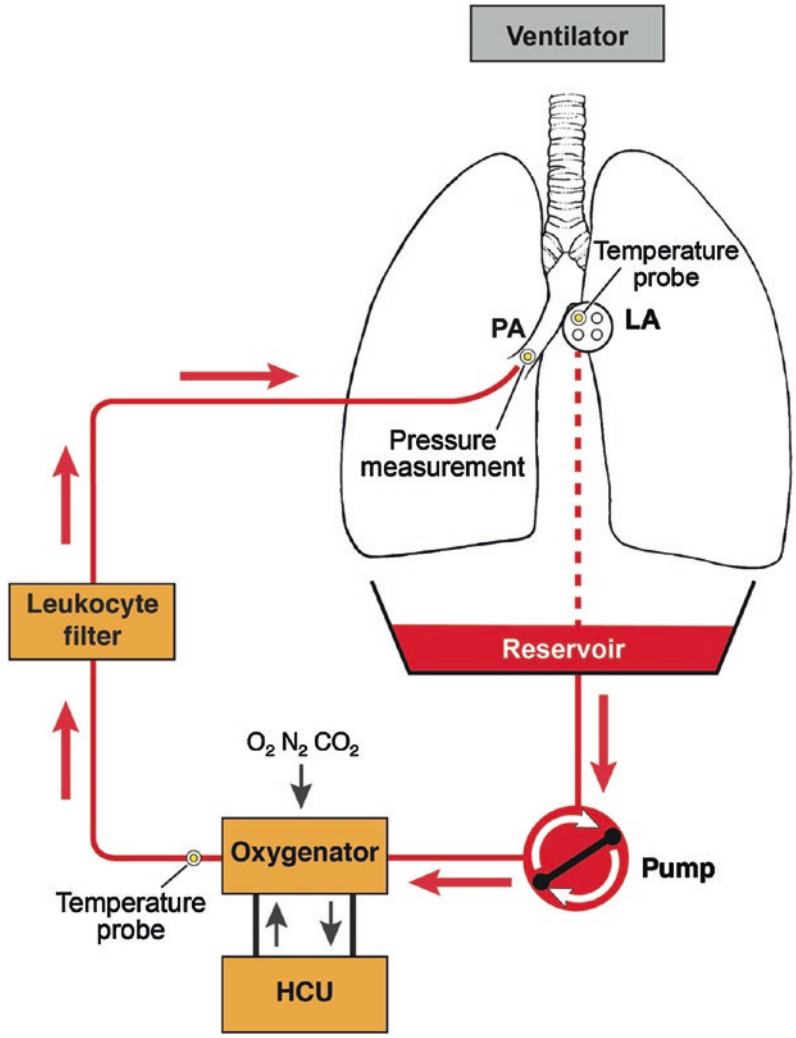

Fig. 1 Schematic diagram of an EVLP circuit. Schematic diagram of an EVLP circuit with the trachea connected to a ventilator and the pulmonary artery (PA) cannulated and perfused. Blood return flows out of the left atrium (LA) and is collected in a reservoir beneath the organ chamber and is pumped through an oxygenator connected to a heater cooler unit (HCU). (Adapted from Wallinder et al. [67])

and ventilate the lung in transit to the recipient hospital. Initial reported results from the INSPIRE trial on standard donor lungs have been promising showing a reduction in primary graft dysfunction grade 3 (PGD3) in the recipient [51]. The subsequent EXPAND trial was conducted to evaluate the efficacy of OCS Lung perfusion and ventilation on donor lungs from ECD and donors after DCD. In this study, 93 lung pairs were perfused and 87% were transplanted. At 72 hrs post-LTx, 44% of recipients had PGD3 which was above the 35% target aim of the study. Post-LTx survival rates were 99% (78/79) at 30-days and 91% (72/79) at 12 months [52]. The study was a single-armed study and no clinical advantage over static EVLP has yet been established. Limitations to the use of the OCS Lung are the costs of the single-use consumables and the need for additional personnel to travel with the retrieval team to the donor hospital.

Fig. 2 **a** Vivoline LS1, **b** XVIVO, **c** TransMedics lung organ care system

Outcomes for Lung Transplant Recipients Using Ex-Vivo Lung Perfusion

The earliest results using the Lund protocol for lungs that were initially considered unusable for transplantation and which were assessed using EVLP reported conversion of six double lung blocks out of nine to successful transplantation [46, 47]. Survival was 100% at 3 months and 66% at 2 years with one patient dying of sepsis and another of rejection. Over 10 years no difference was found in annual FEV1 or 6 minute walk test between recipients of standard donor lung transplants and EVLP lung transplants and there was no difference in survival [53]. Further successful reports were published from Gothenberg [54] and Manchester [55]. A UK

multicentre study investigating the use of EVLP in extended criteria donors demonstrated excess morbidity and mortality in recipients and the study was terminated early [56]. The Toronto technique has demonstrated a good success rate in lungs that were deemed otherwise transplantable. Reported success rates of the Toronto protocol on extended criteria lungs were 50 lung transplants from 58 EVLP procedures from Toronto [49], 9 out of 13 from Vienna [57] and 6 out of 13 from Harefield [58].

Outcomes for DCD Versus DBD Lung Transplantation

The Leuven group compared recipients of DCD lungs (N = 21) with those of DBD lungs (N = 154) and reported no difference in survival, freedom from bronchiolitis obliterans syndrome, acute rejection, inflammatory markers or immediate post-operative survival [59]. They subsequently compared 59 DCD with 331 DBD donor LTx and found comparable freedom from chronic allograft rejection [60]. Levvey et al. reported on 5-year outcomes for the first 72 Maastricht III DCD LTx in the Australian DCD LTx collaborative, describing excellent early and late results and a 28% increase in the number of LTx [61]. Countering these promising results, a 2009 report from the St Louis group reported inferior outcomes in 11 patients undergoing BLTx from DCD donors [62] and a 2016 report from Harefield found that there was a significantly higher incidence of PGD3, lower PaO_2/FiO_2 ratio during the first 24 hours post-LTx and significantly poorer results in terms of BOS-free survival [63]. A 2015 report from the ISHLT registry including 306 transplants from DCD lung donors and compared these with 3,992 transplants using DBD donors. Thirty-day survival was 96% in the DCD group and 97% in the DBD group; 1-year survival was 89% in the DCD group and 88% in the DBD group; 5 year survival was 61% in both groups [41]. More recently 389 DCD LTx out of 20,905 LTx in the United States were reported to have similar 5- and 10-year survival [64]. In an ISHLT registry report, 1,090 DCD LTx out of 11,516 LTx were reported to have similar 5-year survival, although recipient hospital stay was longer for the DCD group [65].

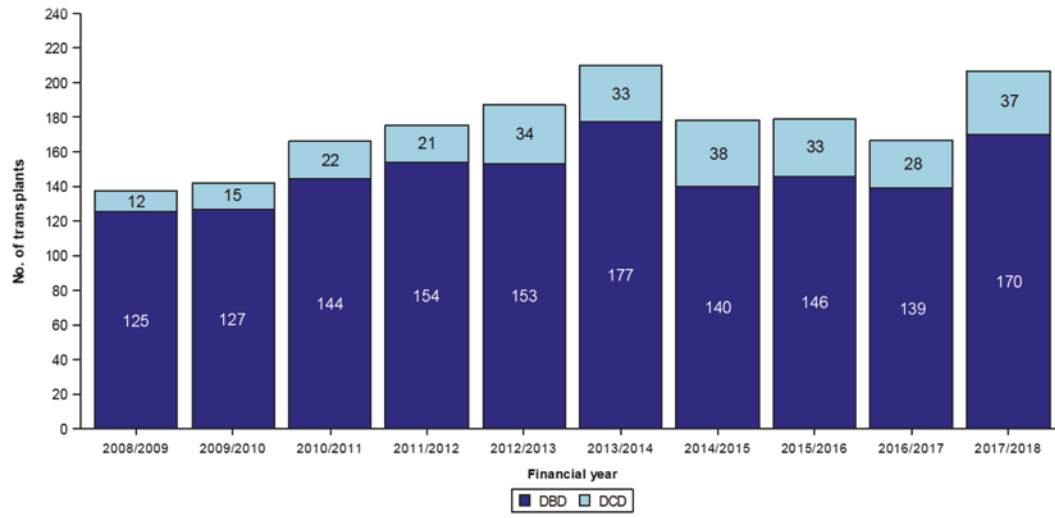

Fig. 3 Number of adult lung transplants in the UK, by financial year and donor type, 1 April 2008–31 March 2018. Graph reproduced from UK Blood and Transplant https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/12300/transplant-activity-report-2017-2018.pdf

Increase in Lung Donation from DCD Donors

In transplant centres contributing to the ISHLT DCD registry, DCD donation has increased from 0.6% in 2003 to 15.2% in 2017 [65]. In the United Kingdom, DCD donors have increased from 288 in 2008–2009 to 619 in 2017–2018, and currently account for 39% of all cadaveric donors. In 2008–2009, 12 out of 137 (9%) lung donors were DCD compared with 37 out of 207 (18%) in 2017–2018 (Fig. 3). In the UK, the donor lung utilisation rate is 16% for DBD lungs but only 6% for DCD lungs. In terms of delivering LTx, the data would suggest that wherever possible, it is preferable for donors who would fulfil brain death criteria to proceed as DBD than DCD since donor organ utilisation is significantly more likely.

Conclusion

Extended criteria lung donors represent a substantial proportion of all cadaveric donors in the current era of LTx. As the waiting list for transplantation increases there will be continued efforts to try and utilise as many donor lungs as possible. Innovations such as DCD have increased the donor pool and the use of both static and portable EVLP technologies will evolve to improve the quality of the donor lung and increase donor organ utilisation rate.

Self-study
In the lung donor the following criteria are absolute contraindications:

1. Age over 65.
2. Smoking.
3. Arterial Blood Gas Analysis PaO_2 < 300 mmHg.
4. Untreated Central Nervous System tumour.
5. Untreated Choriocarcinoma.

In lung donation after circulatory death

1. In hospital transplant recipient recovery times are equivalent.
2. Medium and long-term recipient survival times are equivalent.
3. When compared with donation after brain death lung utilisation for transplant is equivalent.
4. It is obligatory to use EVLP for all DCD donor lungs prior to transplantation.
5. Of potential donors proceeding to withdrawal of life sustaining therapy 90% become asystolic within an acceptable period.

Answers
In the lung donor the following criteria are absolute contraindications…

1. (FALSE) donor age over 65 years is not an absolute contraindication to donation but is associated with reduced recipient survival.
2. (FALSE) donor history of smoking is not an absolute contraindication to donation.
3. (FALSE) an analysis of UNOS data including 12,545 recipients suggests that donor PaO_2 <300 mmHg (20% of donors) and <200 mmHg (15% of donors) had no effect on recipient survival.
4. (FALSE) Untreated Central Nervous System tumours are not an absolute contraindication to transplantation, however, high grade histology Glioblastoma and Meduloblastomas or tumours treated with a previous craniotomy or ventricular shunt or radiation or with recurrent disease in the brain, or a long interval from primary therapy should be considered relatively contraindicated.
5. (TRUE) Untreated Choriocarcinoma is an absolute contraindications to lung transplantation.

In lung donation after circulatory death…

1. (FALSE) In hospital transplant recipient recovery times are not equivalent to transplants from DBD donors with hospital

lengths of stay being reported to be longer in DCD donor LTx recipients.
2. (TRUE) Medium and long-term LTx recipient survival times are equivalent.
3. (FALSE) When compared with DBD (16%) lung utilisation for transplant is inferior in DCD donation (6%) when the outcome of all donors is analysed.
4. (FALSE) The majority of lungs from DCD donation are implanted into the recipient from cold storage.
5. (FALSE) Of potential donors proceeding to withdrawal of life sustaining therapy only 30–40% become asystolic within an acceptable period.

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Bridge to Lung Transplantation

Alexis Slama and Clemens Aigner

Abbreviations

ECLS	extracorporeal life support
ECMO	extracorporeal membrane oxygenation
LTx	lung transplantation
CPB	cardiopulmonary bypass
ISHLT	international society of heart and lung transplantation

Key Points

- "Bridging" to transplantation should be considered for patients on the waiting list suffering from an imminent respiratory or hemodynamic failure
- Device and cannulation technique should be individually tailored to the patient situation
- Awake extra-corporeal membrane oxygenation (ECMO) bridging should be aimed at maintaining a patient's physical status.

Introduction

Extracorporeal life support (ECLS) by means of an extracorporeal membrane oxygenation (ECMO) device is a well-established treatment option for patients with respiratory, cardiac or combined cardiorespiratory failure. Its possible applications have been broadened and above all, its use within the context of lung transplantation (LTx) led to important developments over the last years. In many LTx centers, ECMO has replaced cardiopulmonary bypass (CPB) as the method of choice for intraoperative mechanical cardiorespiratory support [1–5]. Although ECLS has been used early on as a "salvage" strategy to bridge highly compromised patients to transplantation, the high rate of complications led initially to disappointing results [6]. However, present day approaches and modern devices have improved safety and thereby post-operative outcomes. These promising results have in turn led to an increasing use of ECLS as an alternative to invasive mechanical ventilation ("awake" ECMO) and not as an addition to intubation [7–10]. Regarding the respiratory and hemodynamic needs of a patient as well as the anticipated duration of ECLS, different approaches allow for a highly tailored therapy. Most importantly, carefully selected patients can derive a major survival benefit from such an approach while waiting for LTx.

"Bridging" to Transplant

A rapid deterioration of a patient's cardiorespiratory function whilst waiting for LTx bears a high risk of death before a suitable donor organ becomes available. If a patient's respiratory and/

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or circulatory impairment cannot be stabilized sufficiently with conservative treatments, invasive ventilation or ECLS should be considered.

Invasive mechanical ventilation via endotracheal tube or tracheostomy is easily achieved which made it the support of choice in this group of highly debilitated patients. Mechanical ventilation has long been considered a major contraindication to LTx because it is a risk factor for short-term mortality and morbidity. Similar results were observed with ECLS. After a major change in the allocation system by implementation of the LAS score, waiting list mortality dropped significantly and postoperative outcomes of those high-risk patients improved especially in high-volume centers [11]. Both modalities regained popularity.

In most situations, an elective ECMO implantation poses a valid alternative to mechanical ventilation. The ECLS modality of choice depends on the underlying lung disease of the patient and their cardiopulmonary status. As a prerequisite to bridging, the patient should not only meet the inclusion criteria for transplantation but should also have sufficient potential for recovery from later LTx. Patients with prevailing multiorgan failure should be excluded from this possibility as their perioperative risk would surpass their chances of survival. However, those with ventricular failure or temporary congestive liver or kidney insufficiency may be carefully considered if reversibility can be expected after successful transplantation. The International Society of Heart and Lung transplantation (ISHLT) additionally mentions a young patient age as a criterium for ECLS bridging. Those patients have a lower risk of developing complications under ECLS, but a clear age threshold has yet not been defined.

The following algorithm has been suggested to decide whether or not a patient should be bridged to transplant [12]:

(1) respiratory failure is irreversible
(2) patient is still a candidate for LTx
(3) low risk alternatives have been attempted and failed
(4) the patient is likely to receive transplantation during support
(5) support does not increase transplant risk to a prohibitive level
(6) there is a reasonable chance of a successful post-LTx outcome.

If all points can be answered with yes, the current recommendation is to proceed with bridging.

Patient Characteristics

Patients with severely impaired gas exchange are often intubated and ventilated before ECLS is considered [13]. A rapid deterioration occurs most often in cystic fibrosis or interstitial lung disease, eventually putting those patients at a higher risk of severe lung failure compared to patients with emphysema. As stated before, the method of support depends on the circulatory status and the severity of hypoxia and sometimes changes of modality are made necessary by the progression of disease [6].

A clinically relevant pulmonary hypertension and thereby an increased right ventricular afterload can only be resolved by reduction of pulmonary blood flow. Typically, this is achieved by veno-arterial ECMO [3, 14]. Two technically more invasive methods have been suggested as alternatives to this approach but their applicability has yet to be demonstrated in larger patient series before its use beyond experienced centers can be recommended. First, the implantation of a pumpless oxygenator bypassing blood from the pulmonary artery into the left atrium (para-corporal artificial lung) allows for long periods of use and eased mobilization of the patient [15–17]. Secondly, a veno-venous ECMO with additional atrial septostomy improves patient hemodynamics with supposedly less ECLS-related complications compared to veno-arterial ECMO [18, 19].

The indications, the benefits and limitations of each method are summarized in Table 1.

Table 1 ECLS strategies as "Bridge to Transplant"

	PECLA	Central PECLA	Veno-venous ECMO	Veno-arterial ECMO
pCO_2	↓	↓	↓	↓
pO_2	–	↑	↑	↑
PAP	–	↓	–	↓
Indications	pCO_2	pCO_2/pO_2/PAP	pCO_2/pO_2	pCO_2/pO_2/PAP
Duration of treatment	Months	Weeks	Weeks	Days
Invasiveness	+	++++	++	+++
Complication rates	–	++	+	++

PECLA—pumpless extracorporeal lung assist; pCO_2—partial pressure of CO_2; pO_2—partial pressure of O_2; PAP—pulmonary arterial pressure

Modalities of ECLS and Technical Specificities

PECLA (Pumpless Extracorporeal Lung Assist)

These pumpless modalities of extracorporeal oxygenation are solely driven by the arterial-venous pressure gradient of the patient. Manufacturers of different devices use different names (e.g. interventional lung assist—iLA®; $AVCO_2R$—arterio-venous CO_2 Removal) for identical concepts. Although a peripheral pumpless support can be regarded as the least invasive, it requires a patient with stable cardiocirculatory status. Typically, membrane oxygenators with a low resistance and small priming volumes (<200 mL) are used to achieve acceptable flow rates and small foreign body surface areas. With only a fraction of the cardiac output going through the hollow fiber membrane, this approach can only be used to eliminate dissolved CO_2. Flow rates of 500–1000 mL/min are considered sufficient for decarboxylation but the oxygenation capacity is inadequate due to a lower oxygen diffusion rate [20]. In general, cannulation is carried out percutaneously with the Seldinger wire technique using the femoral artery and vein (usually one cannula in each groin) [15]. Further, an additional method has been described as para-corporal artificial lung (PAL; also known as central iLA) where the cannulae are surgically implanted in the main pulmonary artery and in the left atrium [16, 17, 21]. This modality has been successfully used in a limited number of patients suffering from pulmonary hypertension as it allows for both gas exchange and a significant reduction of right ventricular afterload. As the circuit is pumpless, hemolysis is minimal, and the support can be maintained for weeks in waiting patient. Also, central cannulation makes mobilization and ambulation of an awake patient easier than femoral cannulation.

Veno-venous ECMO

In veno-venous ECMO, a centrifugal pump provides a flow rate of up to 4 L/min. In a hemodynamically stable patient, adequate decarboxylation and oxygenation of the blood can both be achieved. Usually, the cannulae are placed through the right femoral vein into the inferior vena cava for drainage (17–21 Fr) and through the right jugular vein into the right atrium for return (15–17 Fr). With the use of a double-lumen cannula placed in the jugular vein, groin access can be avoided, thus allowing for better mobilization of the patient and less puncture site complication [22]. Modern double-lumen cannulas are less invasive and reduce the risk of recirculating oxygenated blood, which can occur if both cannula tips are too close to each other. This phenomenon becomes apparent by a similar color of both circuit limbs.

In severe hypercapnia, veno-venous ECMO (and to a lesser extent a pumpless approach) can lead to an increase in pulmonary arterial pressure after the normalization of the mixed venous pCO_2. Subsequently, right heart insufficiency can develop and has to be treated accordingly.

Veno-arterial ECMO

Veno-arterial ECMO provides a right-to-left shunt through an oxygenator, resulting in a reduction of pulmonary blood flow and unloading of both ventricles. Therefore, in additional to gas exchange, VA ECMO offers systemic circulatory support to patients with ventricular failure. Venous blood is drained either by central cannulation from the right atrium or via femoral cannulation out of the vena cava inferior (17–21 Fr). The oxygenated blood is then returned either centrally to the ascending aorta or peripherally via a main artery (e.g. femoral, subclavian or carotid artery; 15–17 Fr). With femoral arterial return, blood flow is directed retrogradely into the descending thoracic aorta. In some cases, a so-called watershed phenomenon can lead to severe upper body, cardiac and cerebral hypoxemia (the Harlequin phenomenon). For this reason, pulse oximetry should always be measured from the patient's right-hand fingers [1]. In those cases, patients should be administered a higher fraction of inspired oxygen and the ECMO flow should be increased. To reduce the risk of femoral artery obstruction by the arterial canula and consequent distal limb ischemia, placement of an additional leg cannula is strongly advised [14].

"Awake ECMO"—Walking While Waiting

In recent years, an awake ECMO approach has been proven superior to fully sedated ECLS [8–10]. Prerequisites are a cooperative patient and sufficient gas exchange via the oxygenator. Two single lumen cannulae or one double lumen cannula can be placed under local anesthesia. If the patient is already intubated when the decision for ECLS is taken, weaning from mechanical ventilation should be the aim for after ECLS has been set up. The advantages for a spontaneously breathing awake patient are numerous:

- Improved ventilation/perfusion matching (V/Q ratio)
- Avoidance of ventilator induced diaphragmatic weakness
- Improved venous return
- Better expectoration of secretions
- Reduced risk of pneumonia
- Reduced risk of postoperative delirium
- Improved kidney function and fluid balance (trough drug sparing)
- Possible interaction with peers and medical staff
- Active mobilization and training possible
- Possibility of psychological support.

Possible disadvantages and risks are:

- Muscular exhaustion ($O_2\downarrow$, $CO_2\uparrow$)
- Risk of sudden orotracheal intubation
- Risk of (unintentional) self-harm because of the cannulas
- Discomfort, pain, anxiety.

Limitations and Complications

Depending on the invasiveness of the support mode, the concomitant risk of ECLS increases with the duration of support. This is most important for VA ECMO in which complications will inevitably arise within the first weeks [23]. In VV ECMO and pumpless support, successful bridging durations of over a month have been reported [24]. For this strategy to succeed, it is of utmost importance that the patient is prioritized in organ allocation (e.g. with the lung allocation score LAS). Bridging to LTx should ideally be carried out in experienced transplant centers and probably best after elective evaluation and listing of the patient.

The management of patients on ECLS can be complex and multiple factors have to be

Table 2 ECLS bridge to lung transplant—summary of published reports | n.a.: not available; PA/LA: pulmonary artery/left atrium; HD: hospital dismissal

Author	Year	Patients (n; %)			Survival after lung transplant			
		Total	Modalities		Transplanted	30 days	1 year	≥2 years
Lang (Vienna) [23]	2012	38	v. v. v. a. iLA „multiple“	18 (47%) 15 (39%) 1 (3%) 4 (11%)	34 (89%)		78%	5 y: 63%
Toyoda (Pittsburgh) [28]	2013	31	v. v. v. a.	15 (62.5%) 9 (37.5%)	24 (77.4%)	96%	74%	2 y: 74%
Hoopes (Lexington) [29]	2013		“awake”	31 (100%)	31 (100%)		93%	3 y: 80% 5 y: 66%
Schellongowsky (Vienna) [30]	2014	20	v. v. iLA	10 (50%) 10 (50%)	19 (95%)	HD: 75%	72%	3 y: 80%
Inci (Zürich) [31]	2015	30	v. v. v. a. iLA „multiple“ „awake“ Data n.a.	10 (33%) 4 (13%) 5 (17%) 7 (23%) 6 (20%) 4 (13%)	26 (87%)	89%	68%	2 y: 53%
Biscotti (New York) [32]	2017	72	v. v. v. a. Central PA/LA „multiple“	45 (63%) 23 (32%) 1 (1%) 18 (25%)	40	HD: 92.5%	90.3%	2 y: 84%
Hayanga (Pittsburgh) [33]	2018	n.a.	n.a.	n.a.	49	93.9%	81.5%	3 y: 76.9% 5 y: 65.6%
Hakim (Cleveland) [34]	2018	30	v. v. v. a. „awake“	24 (80%) 6 (20%) 8 (27%)	26 (86%)	92%	85%	3 y: 80%
Ius (Hannover) [35]	2018	87	v. v. v. a. v. v. to v.a. „awake“	50 (73%) 25 (37%) 7 (10%) 57 (84%)	68 (78%)		79%	5 y: 65%
Hötzenecker (Toronto) [36]	2018	71	v. v. v. a. Central PA/LA PECLA „multiple“	30 (42%) 7 (10%) 9 (13%) 8 (11%) 13 (18%)	63 (89%)		70%	3 y: 63% 5 y: 51%

taken into consideration to minimize possible complications. Although sufficient anticoagulation can be achieved with low molecular weight heparin, the authors advocate the use of heparin infusion pump for better control. Coagulation values, blood count and markers for hemolysis should be assessed twice daily. According to the most recent registry analysis the most common complications are bleeding (29.8%), infections (17.5%), kidney failure (9.3%), hyperbilirubinemia (8.7%) and neurologic complications (5.9%) [25]. Within the scope of LTx, it is important to mention the increased need for blood transfusion and the associated risk of developing anti-HLA antibodies.

Clinical Evidence

In published registry analyses (1987–2013) ECLS bridging to LTx used to be associated with reduced post-transplant survival (1 year: 50–61%) compared with non-bridged patients (1 year: 79–84%) and patients on invasive mechanical ventilation (1 year: 62–72%) [13, 26]. With LAS allocation, increased case numbers and center experience, outcomes have improved steadily over time. More recent institutional series report 1-year survival rates of 68–90% making those results comparable to the non-bridged patient. Additionally, it has been demonstrated that preoperative ECLS does not impact post-transplant quality of life [27]. An overview of the most recent clinical series is given in Table 2.

Conclusion

Bridging to LTx was always regarded as a "salvage" therapy to keep a patient alive until a suitable donor organ becomes available. Additional to invasive mechanical ventilation, ECLS was utilized in patients with severe cardiopulmonary failure, thus cumulating the risk of both therapies (IMV and ECLS) in patients with an already increased mortality. Improvements of available devices and developments in surgical technique have greatly reduced the associated risks and paved the way for longer bridging durations. More recently, the advantages of an "awake" and "elective" approach have been clearly demonstrated by multiple centers. If possible, patients should be mobilized by means of ECLS rather than immobilized with mechanical ventilation.

Self-study

Bridging with femoro-femoral veno-arterial ECMO (select correct statement):
(1) Bears the risk of unrecognized cerebral hypoxemia in case of inadequate monitoring
(2) Can worsen right ventricular insufficiency after increase of pulmonary vascular resistance
(3) Is an absolute contraindication to an "awake" concept
(4) Is most commonly used in emphysema patients with cardiac comorbidities

"Awake" ECMO (select correct statement):
(1) Can be achieved in all cannulation modalities
(2) Increases the risk of postoperative delirium
(3) Is contraindicated if a prolonged waiting time is expected
(4) Necessitates a "safety" tracheostomy of the patient

Answers

Bridging with femoro-femoral veno-arterial ECMO (select correct statement):
(1) Bears the risk of unrecognized cerebral hypoxemia in case of inadequate monitoring

"Awake" ECMO (select correct statement):
(1) Can be achieved in all cannulation modalities

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Indications and Contraindications in Lung Transplantation

Alexis Slama and Clemens Aigner

Abbreviations

LTx	lung transplantation
COPD	chronic obstructive pulmonary disease
CLAD	chronic lung allograft dysfunction
ILD	interstitial lung disease
A1ATD	α-1 antitrypsin deficiency
LAS	lung allocation score
ISHLT	international society of heart and lung transplantation
IPF	idiopathic pulmonary fibrosis
UIP	usual interstitial pneumonia
NSIP	nonspecific interstitial pneumonitis
PAH	pulmonary arterial hypertension
ECLS	extracorporeal life support
ECMO	extracorporeal membrane oxygenation
PGD	primary graft dysfunction
BOS	bronchiolitis obliterans syndrome

Key Points

- Early referral of patients for lung transplant assessment is key to timely listing and thereby success of transplantation.
- Patients referred for lung transplantation should be evaluated in a case-by-case manner by taking all patient characteristics into account. There are few absolute contraindications. However, numerous relative contraindications have to be considered on an individual basis.
- Patents listed for lung transplantation should be enrolled in rehabilitation programs to optimize their physical fitness and counteract functional limitations.
- Pulmonary re-transplantation should be considered for patients with chronic lung allograft dysfunction (CLAD).

Indications for Lung Transplantation

Patients with end-stage non-malignant parenchymal or pulmonary vascular diseases should be considered for lung transplantation (LTx) when all alternative conservative and surgical treatment options have been exhausted. Referral to a LTx center should be made early when the presumed life expectancy of the patient becomes less than a few years. For LTx to be successful, it is of utmost importance that the patients bear not only a high motivation towards this treatment but also maintains psychological and social stability despite their considerably reduced quality of life.

Of all eligible diagnoses, chronic obstructive pulmonary disease (COPD) has long been the most frequent indication (30.6% of all reported LTx from 1995 to 2017), but was just recently surpassed by interstitial lung diseases (ILD)

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which accounted for 31.3% of all registered transplantations so far [1]. Third in line is cystic fibrosis (15.4%), followed by α-1 antitrypsin deficiency (A1ATD) (4.9%), both occurring in significantly younger patients. Pulmonary arterial hypertension is the most frequent vascular disease leading to LTx. Other indications are depicted in Table 1.

The recent change in the spectrum of diagnoses towards ILD is particularly strong in North America. This development can be attributed to the implementation of the lung allocation score (LAS) in the United States (2005) and within the Eurotransplant region (2011) [1, 2]. The LAS was initially introduced to prioritize patients with a higher mortality on the waiting list by estimating their one-year survival without LTx and their survival after transplantation. Thus, it presumably reflects the "benefit of transplantation" on a 100-point scale [3]. The main parameters which are included in the LAS model are: age, BMI, diagnosis, need for support, diabetes, mechanical ventilation, oxygen treatment, forced vital capacity, pulmonary arterial pressure, carbon dioxide partial pressure and 6-minute walking distance. As per diagnosis groups presented in Table 1, the LAS model currently favors diagnoses in following order: B (vascular diseases) > D (restrictive diseases) > C (suppurative diseases) > A (obstructive diseases).

Regardless of the LAS and other organ allocation mechanisms, selection criteria for LTx candidates have broadly changed over the years. Lung transplantation is a high-risk procedure in a complex patient population, thereby it is of utmost importance to carefully consider all potential contraindications on a case-by-case basis in potential transplant candidates.

So far, the International Society for Heart and Lung Transplant (ISHLT) has published three consensus reports on the selection of lung transplant candidates [4–6]. The 2015 edition and a 2018 review by the same author [7] represent the most up-to-date recommendations in terms of candidate selection and most assertions in this chapter will refer to these.

Table 1 Diagnoses eligible for lung transplantation and their assigned LAS-groups

Diagnoses	% of reported cases [1]	LAS group
ILD (IIP and non-IIP)	31.3	D[a]
COPD	30.6	A
CF	15.4	C
Alpha-1 AT deficiency	4.9	A
Lung re-transplant	4.0	D
IPAH	2.9	B
Bronchiectasis	2.7	A[a]
Sarcoidosis	2.5	A[a] (D[a] if PAP > 30)
Others	5.8	All

ILD interstitial lung disease; *IIP* idiopathic interstitial pneumonia (includes pulmonary fibrosis); *CF* cystic fibrosis; *IPAH* idiopathic pulmonary arterial hypertension; *PAP* pulmonary arterial pressure; diagnosis groups: *A* obstructive airway diseases; *B* diseases of the pulmonary circulation; *C* suppurative lung diseases; D: restrictive lung diseases; [a]special consideration of diagnosis in LAS calculation

Disease Specific Considerations

Interstitial Lung Disease

As interstitial lung disease (ILD) and especially its most common subtype, idiopathic pulmonary fibrosis (IPF) bears the worst prognosis and the highest waiting list mortality, early referral of these patients for assessment at a LTx center is recommended.

The ISHLT consensus suggests referral as soon as one of following criteria is met [6]:

- histopathological or radiographic evidence of usual interstitial pneumonia (UIP) or nonspecific interstitial pneumonitis (NSIP)
- reduced lung function: forced vital capacity (FVC) < 80% of predicted value or diffusion capacity (DLCO) below 40% of predicted value
- need for long-term oxygen therapy (LTOT); also intermittent LTOT during exercise

- lack of improvement under medical therapy.

The listing should take place as soon as one of following criteria is fulfilled:

- decline of lung function within six months: 10% of FVC or 15% of DLCO
- impaired six-minute walking test (6MWT): <250 m distance or 88% SpO_2 or >50 m decline within 6 months
- evidence of pulmonary hypertension
- hospital admission due to respiratory insufficiency, exacerbation or pneumothorax.

Cystic Fibrosis

In CF patients, both the decrease of lung function over time and more recently developed models have been shown similarly predictive for patient survival [8–10]. Additional risk factors which have been identified to negatively impact patient survival include: female sex, diabetes, *B. cepacia* infection, reduced 6MWT—and pulmonary hypertension [10–12].

Referral should be considered in the presence of:

- rapid decrease of FEV1 or FEV1 < 30%
- impaired 6MWT (<400 m)
- evidence of pulmonary hypertension (mean PAP > 25 mmHg)
- increased exacerbation and poor clinical recovery
- acute respiratory failure (with need for non-invasive ventilation)
- increased antibiotic resistances
- pneumothorax
- hemoptysis despite bronchial amortization
- non-tuberculosis mycobacterial disease (NTB) or B. cepacia infection
- frailty and progressive cachexia.

Criteria for listing are:

- chronic ventilatory or respiratory failure ($PaCO_2$ > 50 mmHg, PaO_2 < 60 mmHg)
- long-term ventilation therapy
- pulmonary hypertension (WHO functional class IV).

Emphysema (COPD and Alpha-1 Antitrypsin Deficiency)

Of the common indications for LTx, COPD and alpha-1 antitrypsin deficiency are those with the slowest disease progression and with the lowest short-term mortality. For this reason, it remains unclear at what time listing is most appropriate during the course of disease [13, 14]. Nevertheless, emphysema accounts for a third of all LTx performed worldwide and it seems that those patients mostly benefit from an improved quality of life after transplantation rather than from an increased long-term survival (in the absence of concomitant risk factors). To predict mortality in those patients, the BODE score was developed in a multivariate approach. This is now widely used to identify patients who would benefit from a LTx [15]. Additionally, the frequency of acute exacerbations has been shown to be an independent risk factor [16] and was thereby included in the ISHLT recommendations.

Referral is recommended for:

- progression of disease despite maximum therapy (medication, rehabilitation, LTOT and lung volume reduction)
- reduced lung function (FEV1 < 25%)
- chronic ventilatory or respiratory failure ($PaCO_2$ > 50 mmHg, PaO_2 < 60 mmHg)
- a BODE index ≥5.

The recommendations for listing are:

- a BODE index ≥7
- reduced lung function (FEV1 < 20%)
- a high frequency of exacerbations (≥3 per year)
- a severe exacerbation with need for ventilation
- pulmonary hypertension (WHO functional class III/IV).

Pulmonary Vascular Diseases

Although important advances in the medical treatment of pulmonary arterial hypertension (PAH) have been made in the past 15 years, patient survival of those newly diagnosed remains poor (1-year 86.3%; 5-year 61.2%) [17, 18]. Regardless of their response to medical management, the course of this illness remains unpredictable and an early referral to a transplant center is recommended [19, 20].

Referral should take place for:

- highly impaired patients (NYHA III/IV)
- rapid progression of disease
- patients with parenteral PAH therapy
- patients with veno-occlusive disease or pulmonary capillary hemangiomatosis.

After evaluation, eligible patients should be listed in the presence of one attribute:

- inadequate response to maximum medical therapy, including parenteral prostanoids
- severe hemodynamic impairment (cardiac index < 2 L/min/m^2)
- signs of right heart failure (right atrial pressure > 15 mmHg, effusion/ascites, increase in BNP)
- declining general condition (6-MWT < 350 m)
- development of significant hemoptysis.

Absolute Contraindications

As each transplant center defines its own inclusion rules, there is some disparity regarding which patient condition should be seen as a contraindication. The followings are some of the most common areas of concern and it remains at the center's discretion to weigh up a patient's appropriateness.

Malignancy

A recent history of malignancy can be considered an absolute contraindication as long as the patient has any relevant risk of recurrence. Postoperative immunosuppression leads to an approximately five-fold higher risk of cancer compared with the general population [21], thus any malignant disease has to be excluded before considering a patient for listing. In skin cancer other than melanoma, a two-year disease-free interval can be considered sufficient. In other entities such as blood, breast, kidney, bladder or sarcomatous malignancies, a recurrence-free interval of at least five-years should be reached.

Organ Failure

Relevant extra-pulmonary organ failure is a contraindication for LTx except for temporary congestion-induced kidney failure in PAH patients which is considered to be reversible. Nevertheless, in selected patients, multi-organ transplantation can be considered. Typical combinations include heart-lung transplantation for PAH secondary to congenital heart disease or lung-liver transplantation in patients with cystic fibrosis.

Compliance

Psychosocial well-being such as adherence to medical therapy are of utmost importance for the survival of the transplant recipient and the graft. Patients with a known history of non-compliance or patients with a psychological or psychiatric illness making them unable to comply with the post-transplant medical regimen should be excluded from LTx.

Mental Disorders

Although postoperative psychiatric status is associated with an increased morbidity and mortality, patients should be adequately treated and supervised during the time on the waiting list and not sweepingly considered unfit for transplantation [22, 23]. In less severe mental disorders such as depression or anxiety, which often occur in chronically ill patients, subclinical symptoms tend to improve after successful LTx [22].

Functional Limitations

Most patients referred to a transplant center will have a considerable degree of reduced general condition (see → frailty). However, any functional limitation making a rehabilitation program pre- and post-transplant impossible (e.g. in musculoskeletal disorders or neurodegenerative diseases) should be considered an absolute contraindication.

Substance Abuse

Ongoing substance abuse and/or dependence (e.g. tobacco, alcohol, cannabis, benzodiazepines, opiates or other illicit substances) should be excluded before offering lung transplantation. If necessary, sound evidence of a patient's long-term abstinence should be required before listing. The duration of mandatory nicotine abstinence various between centers (usually 6–12 months). Repeated blood or urine tests for cotinine can be easily carried out when in doubt.

Relative Contraindications

Age

Available literature often mentions a maximum age of 65 years. Although a higher patient age is associated with less physical reserve and a higher incidence of other comorbidities, a patient's fitness should always be considered in terms of his biological age. So far, all reports on recipients up to 70 years of age have demonstrated that post-operative results are comparable to younger ones in carefully selected patients [24–26].

BMI

An optimal nutritional status is associated with improved post-transplant outcomes. Significantly undernourished patients have an increased risk of postoperative infection and ultimately a worse survival [27]. Nevertheless, only progressive or extreme cases should be declined for transplant. In those patients, most often suffering from CF, a specialized nutritional support remains equally important before LTx as after [28] and all efforts should be made to improve their nutritional status.

Frailty

Although frailty is very common in LTx candidates, it was only recently acknowledged as an independent risk factor. So far, there is no consensus as to the best frailty quantification measure, but two established scores have been suggested in the context of LTx (SPPB: Short Physical Performance Battery and FFP: Fried Frailty Phenotype). Although frail patients are at a higher risk of delisting prior to LTx [29] and death within the first year after transplantation [30], it is acknowledged that in most cases, frailty will resolve after transplantation. Thereby, frailty alone should not be seen as an absolute contraindication for LTx [31].

Coronary Artery Disease

Patients with a history of myocardial infarction should not be offered a LTx due to the high perioperative risk. For coronary artery disease (CAD), opinions remain mixed. The concerns are based on the fact that immunosuppression may accelerate coronary atherosclerosis [32] and that patients with CAD may by themselves have limited survival [33]. Nevertheless, several recent reports suggest that pre-transplant or concomitant revascularization (either by percutaneous coronary intervention or surgical revascularization) is associated with acceptable outcomes comparable to those of patients without CAD [33–36].

Obesity

Obesity is associated with a higher risk after transplantation, whereas weight loss before LTx showed improved short- and long-term clinical outcomes [37, 38]. Current recommendations refrain from listing patients with a class II or III obesity (BMI $\geq$ 35.0 kg/m^2) and suggest

rigorous weight loss and treatment of obesity related comorbidities.

Other Medical Conditions

An unstable medical condition as acute sepsis, liver failure, uncontrolled bleeding disorder or recent infarction should be treated before further course of action. The same applies to insufficiently controlled viral or microbial infection or proof of active tuberculosis.

Bacterial/Fungal Infection

An extrapulmonary colonization or infection with highly resistant fungi or bacteria which can potentially worsen after transplantation has to be carefully considered. Special mention should be made for *Burkholderia cenocepacia, Burkholderia gladioli* and *Mycobacterium abscessus* where an insufficient post-operative control is associated with a significantly higher mortality [39–41].

HIV/Hepatitis

Although infection with hepatitis B or C was initially considered an absolute contraindication for LTx, recent reports have demonstrated unimpaired patient survival after interferon free treatment [42, 43]. Nevertheless, patients should be evaluated for any signs of cirrhosis and portal hypertension. Pharmaceutical therapy of those patients should be carried out in association with an experienced hepatology unit. Similarly, patients with well-controlled HIV infection have been reconsidered for LTx. So far, only a few patients have been reported on and the general consensus is that patients with undetectable HIV-RNA and no acquired immunodeficiency syndrome should not be categorically excluded from any solid organ transplantation [44, 45].

Chest Wall Deformities

Chest wall or spinal column deformities can be a contraindication for LTx if breathing mechanics are likely to be relevantly impaired after transplantation. Patients with idiopathic fibrosis or cystic fibrosis are prone to severe kyphosis or scoliosis and the surgical decision can only be made on a case-by-case evaluation. Successful transplantations have been reported in patients with thoracic cage flatness, scoliosis and pectus excavatum which was concomitantly corrected during LTx [46–48].

Other Conditions

Other medical conditions such as osteoporosis, arterial hypertension, arteriosclerosis, hypo- and hyperthyroidism, epilepsy, tachyarrhythmia, obstructive sleeping disorders, hyperlipidemia, kidney insufficiency, peripheral arterial occlusion, gastro-esophageal reflux disease, immunodeficiencies and others may potentially worsen after transplantation or significantly impact survival after LTx. Nevertheless, they should be addressed properly before listing and if treated accordingly, should not be considered a contraindication for transplantation.

Surgical Considerations

Any prior intrathoracic and intrapleural interventions (chest tube, thoracoscopy, thoracotomy sternotomy) will to a certain extent lead to pleural adherences. Those can vary from minimal “spider-web” adhesions (as after chest tube placement for pneumothorax) or severe complete pleural fusion (e.g. following pleurectomy or pleurodesis). In the latter patients, an increased peri-operative risk and a higher rate of bleeding complications during LTx has been described. Nevertheless, mid- and long-term outcomes remain unaltered by previous surgery or pleurodesis, making those interventions not contraindications for LTx.

Pneumonectomy

Very rarely, patients who had previously undergone a pneumonectomy are referred for consideration of LTx. Although the changes in mediastinal anatomy after pneumonectomy would render a subsequent contralateral transplantation technically more difficult, those

patients should be considered for transplantation. Few reports exist about the outcomes of such a therapeutic sequence and although perioperative morbidity and mortality was significantly higher, no significant differences were observed in long-term survival [49–52]. Recently, a case report was published describing a bilateral pneumonectomy for the treatment of pulmonary septic shock, followed by 10-day ECMO bridging and subsequent successful lung transplantation as a proof of concept [53]. This option could be considered for highly selected patients.

Lung Volume Reduction Surgery (LVRS) and Endoscopic Lung Volume Reduction (ELVR)

Endoscopic lung volume reduction (ELVR) is mostly performed by implanting either metallic valves or coils into the segmental bronchi of patients with emphysematous lungs. Alternative methods involving endobronchial instillation of water vapor or sealants are not yet established and any evidence in the context of LTx is still missing. Aside from a few case reports, only two published retrospective series address ELVR prior to LTx [54, 55]. Although those patients showed a significantly higher rate of bacterial colonization after LTx, no negative impact on LTx outcomes could be seen after previous ELVR, making it safe for subsequent LTx. The impact of lung volume reduction surgery (LVRS) before LTx has long been debated as pleural adhesions seemed way more severe after extensive pleurectomy or the use of stapler buttressing (made out bovine pericardium). To reduce any risk of phrenic nerve palsy in cases where the mediastinal pleura is adherent, it has been suggested that the visceral pleura is left on the nerve and to just dissect the parenchyma in this area during the pneumonectomy [56, 57]. LVRS prior to LTx does not impair long-term outcome after LTx and can be used to delay the time of listing for LTx [55, 57].

Extracorporeal Life Support (ECLS)

Although initial experiences with ECLS prior to LTx were rather discouraging, ongoing developments in technology has led to very promising results of a “bridge to LTx” strategy [58]. This topic is explored in more detail in another chapter of this book.

Re-transplantation

Pulmonary re-transplantation has reportedly been performed in three very distinct situations: early graft failure as a result of primary graft dysfunction (PGD), severe airway complication and bronchiolitis obliterans syndrome (BOS) as the most frequent indication [59–64]. In early graft failure, outcomes of subsequent re-transplantation were very poor across all reports (50–53% 1-year survival) and listing of non-ambulatory patients who have not been weaned from a ventilator or ECMO after primary LTx is not advisable [63, 65]. Lung re-transplantation for airway complications remains controversial. Re-transplantation for airway dehiscence has a similarly low success rate as for PGD [66], whereas re-transplantation for untreatable airway stenosis was associated with excellent survival rates [59, 64]. Although lung re-transplantation for BOS has historically had a significantly worse outcome than for primary LTx, more recent reports from high-volume centers have shown comparable survival rates [59, 66].

The scarcity of available donor organs is a significant ethical issue when considering pulmonary re-transplantation. Therefore, it is important to identify patients who would most likely benefit from re-transplantation. Nevertheless, the criteria which apply to candidate selection can be adopted from those for primary transplantation. Taking into account currently published data, lung re-transplantation should be carried out solely in experienced centers.

Conclusion

Pre- and post-operative morbidity and mortally, as well as risk factors and waiting time varies greatly between different indications for LTx. Thorough knowledge and understanding of these different characteristics will provide the appropriate patient with the best chance of receiving a lung transplant with the optimal outcome.

Self-study
The lung allocations score (LAS):

(1) Automatically increases with waiting time.
(2) Does not consider physical fitness.
(3) Favors rapidly progressing diseases over slowly progressing emphysema.
(4) Takes the quality of the donor organ into account.

Which condition should be considered an absolute contraindication for lung transplantation?

(1) Bilateral lung volume reduction with pleurectomy.
(2) Coronary artery disease requiring revascularization.
(3) Higher age of 69 years.
(4) Schizoaffective disorder with history of non-adherence to therapy

Answers
The lung allocations score (LAS):

(3) Favors rapidly progressing diseases over slowly progressing emphysema

Which condition should be considered an absolute contraindication for lung transplantation?

(4) Schizoaffective disorder with history of non-adherence to therapy.

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Approaches and Surgical Techniques in Lung Transplantation

Antonios Kourliouros and Steven Tsui

Key Points

- Operative planning of lung transplantation should be individualised to the patient's pre-operative characteristics, disease process and experience of the surgical team.
- Less invasive approaches and avoidance of cardiopulmonary bypass may be employed in selected patient groups.
- Careful dissection and meticulous anastomoses of the hilar structures ensure optimal short- and long-term outcomes.

Introduction

In lung transplantation, the operative plan is made following surgical consultation with the patient. Although there are no universally accepted guidelines, the presence of severe pulmonary hypertension or cardiac dysfunction are often indications for using intraoperative mechanical cardiopulmonary support. The need for concomitant cardiac procedures, or for extensive dissection of pleural adhesions where blood conservation may be necessary, are some of the situations where the use of conventional cardiopulmonary bypass (CPB) may be considered.

It is not uncommon that the surgeon performing the transplant may not be the one responsible for the original consultation and the operative planning. The operative plan is instructive but not rigid as personal preferences and experience of the operating surgeon could influence the final decision. The objective should be for every patient receiving lung transplantation to have an uneventful and uncomplicated operative course, providing them with the best chance of a good short- and long-term result.

Approaches to the Chest for Lung Transplantation

– Sternotomy: Sternotomy is a very familiar approach to the cardiothoracic surgeon providing excellent and prompt exposure of the heart and great vessels. It is well tolerated by the patient in terms of post-operative pain and provides superior chest wall mechanical function compared to thoracotomies [2]. However, there are some limitations of median sternotomy. Firstly, it can be difficult to access apical, posterior and diaphragmatic adhesions. Therefore, most transplant units

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will carefully screen for extensive pleural scars prior to embarking upon lung transplantation with this approach. Secondly, the orientation of hilar structures is such that extensive manipulation of the heart is required and haemodynamic stability can only be achieved with the use of CPB, with very few exceptions. Access to the left hilum can be challenging via this approach, due to the left ventricle extending over it. Retracting the fibrous pericardium towards the right side or even application of apical suction devices to the heart has been utilised to facilitate the left-sided anastomoses. Using hand-held lung retractors covered with surgical gauze to retract the heart can occasionally injure the epicardial vessels and myocardium.

– Bilateral thoracotomy: Sternum-sparing bilateral thoracotomies for lung transplantation range from extensive posterolateral ones to the 'less invasive' sub-mammary anterior thoracotomies. The latter is becoming more popular in selected patients, supported by encouraging results published in the literature [3] but also from the superior cosmetic effect compared to other approaches. The patient is placed in a supine position with the arms by the side. It is not uncommon to opt for arm abduction and support over the head, and a 45-degree tilt of the dependent scapula; this may improve access but will require performing similar manoeuvres to position the contralateral side upon completion of the ipsilateral transplant, while maintaining sterility. The skin incision is made in the 5th intercostal space (or sub-mammary for female patients) and is often no longer than 12–15 cm. Entry into the pleural cavity is usually via the 5th intercostal space with the exception of restrictive lung disease where the 4th intercostal space may be preferable. The intercostal muscles are divided with diathermy to the posterior axillary line, allowing for tension-free opening of a rib retractor without causing fractures. This approach provides satisfactory access to the hilum but less so to the apex and lateral surface of the lung, which can be a limitation in case of extensive pleural adhesions. A heavy retraction suture can be placed in the dome of the diaphragm and exteriorised under tension through a stab incision, which can be later used for introduction of a vascular stapler and chest drain upon completion of the procedure. This manoeuvre can help flatten the diaphragm and increase the available working space, especially in cases of pulmonary fibrosis with a restricted pleural cavity. With the anterior thoracotomy approach, the surgeon still has to operate through a limited access and relies heavily on the assistant despite them not always having direct vision of the operating field.
– Clamshell (bilateral transverse thoracosternotomy): Bilateral anterior thoracotomies in the 4th intercostal spaces that are connected with a transverse sternotomy. The internal thoracic arteries and veins are identified, ligated and divided. The intercostal muscle incision is extended to the posterior axillary line on either side but the latissimus dorsi and serratus anterior muscles are spared. Excellent surgical exposure is offered by this approach but it has to be weighed against the impact of postoperative pain and impaired chest wall mechanics, which may translate to inferior postoperative pulmonary function as shown in an observational study of clamshell versus bilateral anterior thoracotomies [3].

Anatomical Principles of Lung Transplantation

Explant

Explant of the diseased native lung is effectively an intrapericardial pneumonectomy. Following chest wall incision, the pleura is opened and the native lung is deflated. To mobilise the lung, the pulmonary ligament and any pleural adhesions are divided with electrocautery. The phrenic nerve must be identified and preserved when the pleural reflection is incised over the hilar structures to reveal the pulmonary artery

and veins. These vessels can be traced laterally along their lengths using blunt dissection. The fibrous pericardium is then opened anterior to the pulmonary veins (PV) and this incision is extended circumferentially around the left atrial cuff formed by the PV confluence. Once the PVs are dissected free, they are encircled with heavy silk ties. The pulmonary artery (PA) lies within a loosely adherent adventitial sleeve of tissue. If a vascular clamp was inadvertently applied on the outside of this adventitial sleeve instead of on the wall of the PA, the stump of a divided PA could slip back through the vascular clamp with potentially disastrous consequence. The correct dissection plane is entered by cutting through this 'yellow-pink' adventitial sleeve with scissors to reach the glistening white surface of the PA which is said to resemble '*the white of the eye*'. Temporary snaring of PA using an umbilical tape could be used to assess for haemodynamic instability and/or excessive rise in the PA pressure. This can serve as a useful test to determine the need for cardiopulmonary support prior to dividing the PA. The PA can be clamped proximally, its branches tied distally and transected just proximal to the upper lobe branch. Alternatively, it could be stapled transected with an Endo GIA (Covidien, MN, USA) vascular stapler. The PVs are divided as above leaving as much length on the recipient's left atrium as possible. The peri-bronchial soft tissue is dissected off the distal main bronchus with scissors or electrocautery, taking care not to denude and devascularise its proximal length. The cartilaginous bronchus is transected flush with the mediastinum using a No. 11 scalpel blade. Retraction sutures are placed at the 3 and 9 o'clock positions of the proximal bronchial cut edges using 4-0 polydioxanone (PDS II, Ethicon, NJ) sutures. The membranous bronchus posteriorly is then divided. The rest of the hilar tissue behind the transected bronchus is divided very close to the lung and away from the posterior mediastinum in order to minimise the risk of vagal nerve injury. The pneumonectomy is complete and the native lung can be removed from the operating field. Bleeding bronchial artery stumps and mediastinal lymph nodes are ligated or cauterised to ensure complete haemostasis. A taurolidine pleural lavage should be routinely performed in patients with septic lung conditions such as bronchiectasis or cystic fibrosis as this may reduce subsequent colonisation of the transplanted lung [4]. It is very important that the atrial cuff and the PA stump are fully mobilised to allow for the secure grip of the atrial and arterial clamps respectively, and to provide enough tissue for comfortable and tension-free anastomoses during implant.

Implant

The bronchial anastomosis is performed first and is the key determinant of early and longer-term success of lung transplantation. The lung is unique in solid organ transplantation in that it loses its systemic arterial blood supply because the bronchial arteries are not routine revascularised. The donor lung relies only on the pulmonary artery for blood supply once transplanted. Whilst this is sufficient for the lung parenchyma, blood supply to the donor bronchus is rendered precarious making this the Achilles' heel of the procedure. For this reason, the donor bronchus should be trimmed back to 1 cartilaginous ring away from the lobar divisions, minimising the bulk of the non-vascularised tissue. The 4-0 PDS retraction sutures previously placed in the recipient bronchial stump are now used for continuous suturing of the bronchial anastomosis, starting from the junction of the cartilaginous and the membranous portion (Fig. 1). Telescoping of the anastomosis is advocated by some as a means of reducing airway complications. Likewise, use of an omental or pedicled vascular flap to promote anastomotic healing have been utilised but with equivocal outcomes. We believe that care taken to avoid devascularising the bronchus and symmetric approximation of the donor and recipient ends are the keys to a successful bronchial anastomosis. A fibre-optic bronchoscopy is performed immediately after completion of each bronchial anastomosis.

A Satinsky clamp is applied on the left atrium allowing for a generous cuff. On the

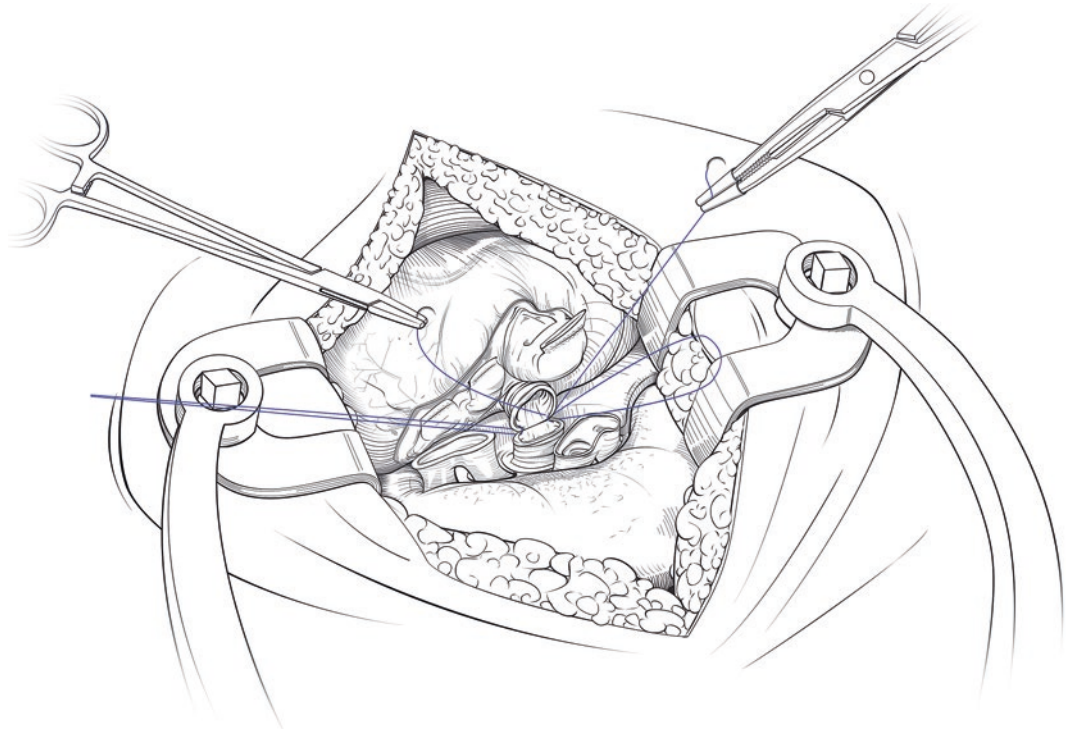

Fig. 1 Intraoperative view of left lung implantation through left anterior thoracotomy—bronchial anastomosis

right, incising the interatrial fat pad can help provide an extra 6–8 mm of left atrial tissue. Both PV stumps are then excised and the connecting bridge of atrial tissue in between is divided to give a single wide opening. Everting suturing is used to approximate the donor and recipient left atrial cuffs to create an uninterrupted approximation of the atrial endothelia, minimise the risk of thrombus formation (Fig. 2). A continuous 3-0 polypropylene suture is used and its ends are left untied for later de-airing upon completion of the PA anastomosis.

The success of the PA anastomosis is determined by ensuring no excess length which could cause a kink or stenosis and the accurate orientation of the donor and recipient stumps to avoid twisting (Fig. 3). Problems of the PA anastomoses are the most common of the vascular complications, which occur in 2–5% of patients undergoing lung transplantation, and the associated mortality often exceeds 50% [5]. Excess donor PA should be trimmed back to the origin of the upper lobe branch. The PA anastomosis is performed using a continuous 4-0 or 5-0 polypropylene suture. On completion, the PA suture line is left loose. The Satinsky clamp on the left atrial cuff is partially released to de-air through the left atrial suture line and to flush the lung preservation solution back out of the open PA suture line. The atrial clamp is re-applied, and the PA clamp is slowly released for antegrade flushing and de-airing through the LA suture line. Both sutures are then tied and all the clamps are removed. Protective ventilation is initiated and haemostasis is secured (with emphasis to donor pericardium as well).

Off-Pump

Single and bilateral sequential lung transplants can both be performed without mechanical circulatory support thus avoiding the complications associated with its use. However, the surgeon and anaesthetist must be ready to address any major physiological changes during

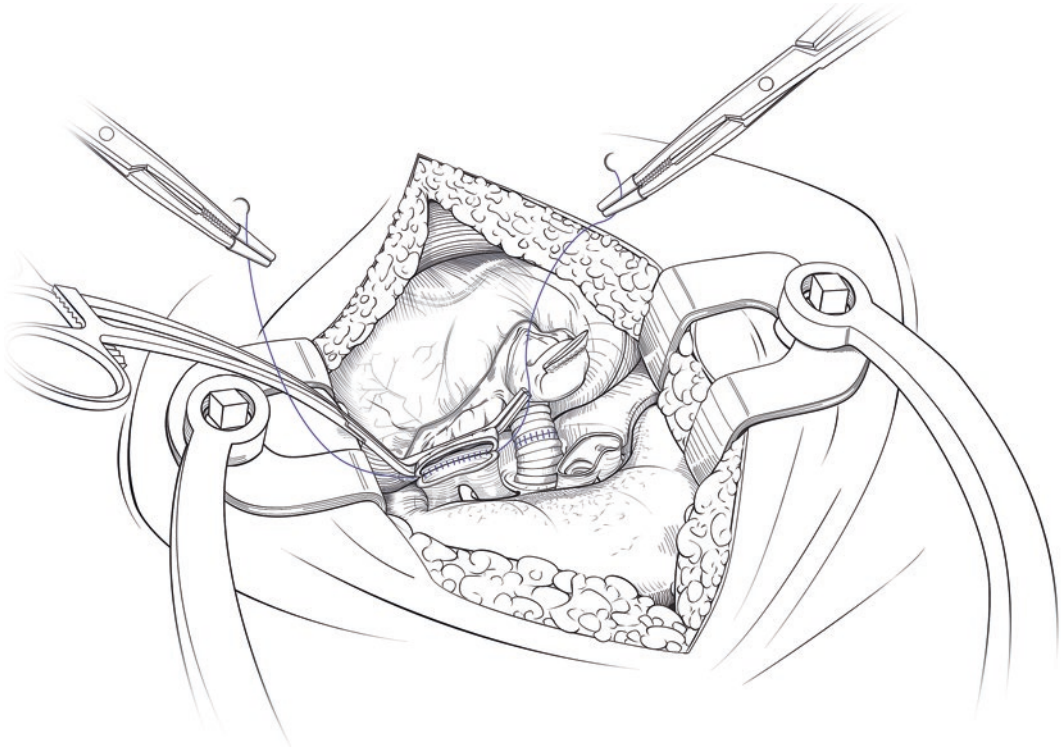

Fig. 2 Intraoperative view of left lung implantation through left anterior thoracotomy—atrial cuff anastomosis

the recipient pneumonectomy. Single lung ventilation may lead to significant hypoxia, especially before the PA of the unventilated lung could be clamped. Manipulations to isolate the atrial cuff may lead to arrhythmias with haemodynamic consequences. Finally, clamping of the PA increases the right ventricular afterload and, in the presence of pre-existing pulmonary hypertension, can result in haemodynamic collapse. Patient selection is therefore the main determinant for the success of off-pump lung transplantation. The criteria are not stringent and vary between surgical teams and institutions. Pulmonary hypertension, presence of right ventricular dysfunction and severe native lung disease are some of the relative contraindications for this approach. Temporary lung isolation, as well as test clamping of the PA could inform the team as to whether an off-pump approach is feasible before committing to the ligation of the hilar structures. Decision on which side the transplant should be performed first depends on the preoperative functional assessment of each lung, aiming to start with the one exhibiting the worst performance. Finally, unplanned conversion to CPB is associated with increased mortality in lung transplantation and should be avoided [6].

Using Cardiopulmonary Bypass

In off-pump lung transplantation, after occluding the pulmonary vessels of one lung, the patient would rely on the remaining lung for adequate cardiac output to flow through and for gas exchange. In certain conditions such as severe pulmonary hypertension or very non-compliant lungs, the patient may not tolerate single lung ventilation-perfusion. Cardiopulmonary bypass provides haemodynamic stability and can maintain the systemic circulation and oxygenation whilst offering blood conservation during lung transplantation.

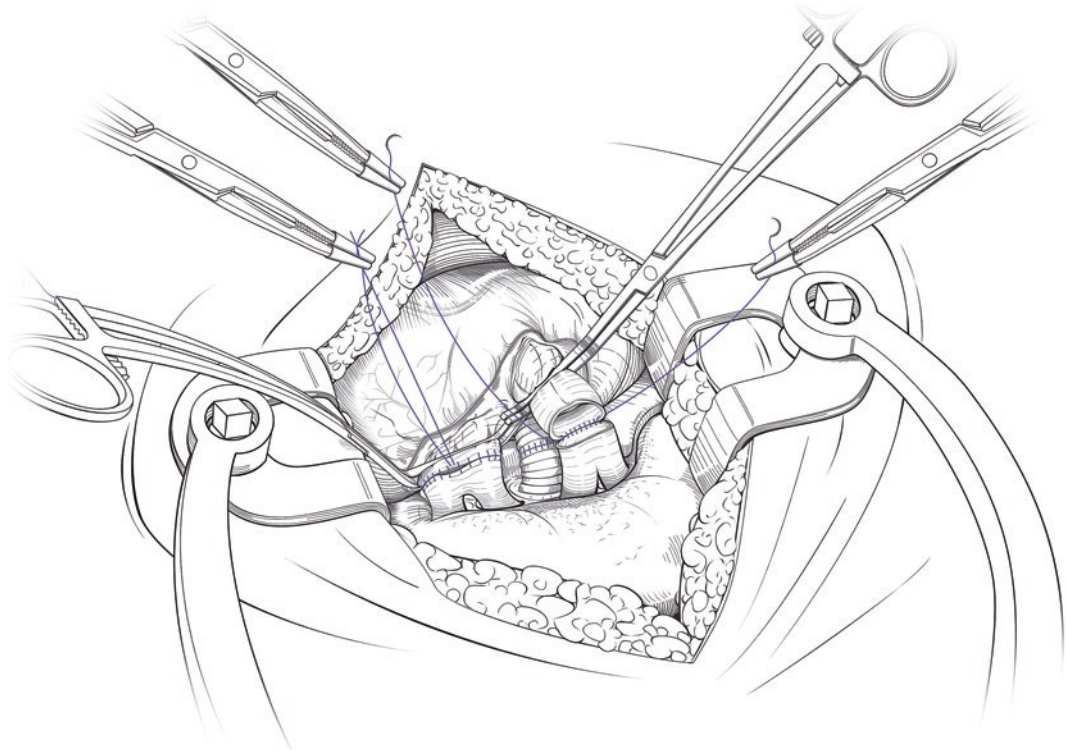

Fig. 3 Intraoperative view of left lung implantation through left anterior thoracotomy—pulmonary artery anastomosis

This can be an invaluable tool for subgroups of patients with anticipated difficulties with single lung ventilation, or for use where extensive and potentially haemorrhagic explants are expected (e.g. previous thoracic surgery, pleurodesis etc.).

During CPB, anastomoses of the atrial cuffs and the pulmonary arteries can be performed with an open technique, i.e. without the use of the vascular clamps on the recipient side. This can be useful in cases where the amount of recipient atrial tissue is limited or access to apply a vascular clamp is restricted. Open vascular anastomoses can take place with the heart arrested but also on the beating heart subject to appropriate venting to avoid cardiac ejection during the procedure and thorough de-airing manoeuvres before lung reperfusion.

Pitfalls of Cardiopulmonary Bypass

It is well recognised that CPB induces a systemic inflammatory response and blood component damage, leading to more postoperative bleeding and use of blood products. Avoidance of blood products and more specifically, platelet transfusion, is pertinent in lung transplantation.

Full CPB with the beating heart (but not ejecting) or with the heart arrested and the aorta clamped has some potentially important implications:

– In bilateral sequential lung transplantation, the first lung implanted would remain unperfused until the contralateral lung implantation is complete and CPB weaned off, potentially

resulting in prolonged warm ischaemia for the first lung. Primary graft dysfunction and complications of the donor bronchus are associated with prolonged ischaemia and these need to be considered.
– Some surgeons perform bilateral pneumonectomies before proceeding with lung implantation. Although this could potentially optimise time management and reduce warm ischaemic time of the first implanted lung (as mentioned earlier), the heart chambers should be vented or the vascular stumps left open to avoid blood stasis within these structures.

Finally, if only a two-stage cannula was inserted in the right atrium for venous drainage, the SVC could be compressed when retracting the right hilum, compromising upper body venous return. Therefore, increases in central venous pressure or poor venous return to the CPB reservoir should not be ignored or just compensated for by adding volume to the circuit. An additional venous drainage cannula should be added to splint open the SVC.

Use of Venoarterial Extracorporeal Membrane Oxygenation (VA ECMO)

The inflammatory response associated with CPB may be ameliorated by using a closed circuit and avoidance of the venous reservoir and cardiotomy suckers i.e. venoarterial extra-corporeal membrane oxygenation (VA ECMO). This also results in a reduction in the use of blood and blood products after cardiac surgery. VA ECMO provides comparable haemodynamic support and gas exchange to CPB but has the advantage of requiring a lower level of anticoagulation. However, the flow rate is affected by fluctuations in venous return; spilt blood has to be cell-saved rather than directly returned to the circuit and the circuit has susceptibility to air lock, and hence precludes the ability to perform open anastomoses. Current observational evidence supports the use of VA ECMO over CPB with regards to short-term outcomes such as transfusion and renal complications [7]. In our practice, when mechanical circulatory support is contemplated in cases of bilateral anterior thoracotomies, peripheral VA ECMO is established with flows calculated to provide adequate tissue perfusion and oxygenation, while allowing for some cardiac ejection to ensure perfusion of the first transplanted lung.

Decision Making in Choice of Incision and Extracorporeal Support

A sternotomy approach invariably requires some form of cardiopulmonary support, whether central CPB or peripheral VA ECMO. Mediastinal retraction to access the right hilum can obstruct the SVC and increase the central venous pressure. Inserting an additional cannula in the SVC is often recommended to facilitate venous drainage of the head.

The bilateral anterior thoracotomy approach is often combined with an off-pump technique aiming for better chest wall stability, avoiding the detrimental effects associated with CPB and improved cosmesis. In cases where cardiopulmonary support is required, many units advocate the use of peripheral VA ECMO. This provides the necessary haemodynamic and respiratory supports with the benefit of less bleeding (lower activated clotting times required compared to conventional CPB) and some perfusion into the transplanted lung enabling earlier reperfusion. Central cannulation cannot be performed with the bilateral anterior thoracotomy approach unless it is converted to a ‘clamshell’ which is the most versatile incision with regards to CPB options. The ‘clamshell’ approach allows for off-pump as well as any other type of central cardiopulmonary support.

Conclusions

The choice of surgical access and cardiopulmonary support in lung transplantation has to be individualised and viewed through the experience and training of the surgical and anaesthetic teams. In the multidisciplinary assessment of

the lung transplant candidate, the responsible surgeon will draft the operative plan which will subsequently be agreed upon following review of all the investigations and communicated with the rest of the team. Local protocols should be in place to ensure consistent practice. Unplanned conversions to CPB, and prolonged warm ischaemic times or postoperative bleeding, both of which are often result of poor surgical access, are associated with adverse outcomes and should be avoided. In this chapter we have highlighted key technical aspects of lung transplantation which should mitigate the above and assist in the decision making and safe conduct of this procedure.

Self-study

1. Which of the following statements in lung transplantation surgery is true?
   a. Generous amount of donor and recipient bronchus is necessary to obtain a good quality bronchial anastomosis.
   b. Ensure very snug knot of the pulmonary artery anastomosis upon its completion.
   c. Allowing for myocardial tissue between the approximation edges of the two atrial cuffs has no effect in the quality of the transplant.
   d. Antegrade and retrograde flushing of pneumoplegia and venting is an essential manoeuvre in off-pump lung transplantation.

2. Which type of access to the chest is NOT paired with the type of cardiopulmonary support described:
   a. Bilateral anterior thoracotomies with central (right atrial to aorta) cardiopulmonary bypass.
   b. Bilateral anterior thoracotomies with peripheral (femoral vein to femoral artery) VA ECMO.
   c. Median sternotomy with peripheral (femoral vein to femoral artery) full cardiopulmonary bypass.
   d. Bilateral transverse thoracosternotomy (clamshell) with central (right atrium to aorta) cardiopulmonary bypass.

3. Which one of the following statements is correct in bilateral sequential lung transplantation without the use of cardiopulmonary bypass support?
   a. The procedure should start on the side where the lung has the higher perfusion ratio.
   b. The need for blood and blood products is often less without the use of full cardiopulmonary bypass.
   c. Extensive pleural adhesions the disruption of which leads to air leak and excessive blood loss do not influence the safe conduct of off-pump lung transplantation.
   d. The need for de-airing upon completion of the anastomosis is not necessary in off-pump lung transplantation.

Answers

Question #1

A. Incorrect: Both the recipient and donor bronchi should be trimmed to the shortest length possible to allow for a tension-free anastomosis while minimising the amount of devascularised tissue.

B. Incorrect: Purse-string effect by overtying the PA anastomosis may be responsible for subsequent stenosis and graft failure.

C. Incorrect: A good anatomical approximation of the donor and recipient atrial cuffs, eliminating any redundant tissue between the endothelial surfaces is the key to the avoidance of thrombi and potential embolic material.

D. Correct: Manoeuvres for removal of lung preservation fluid and venting prior to release of the atrial and arterial clamps is important for avoidance of its systemic effects and air embolisation.

Question #2

A. Correct: Access to the ascending aorta and the right atrium for central cannulation is compromised when utilising bilateral anterior thoracotomies and therefore not performed.

B. Incorrect: Peripheral cannulation and establishment of VA ECMO or cardiopulmonary bypass is feasible and occasionally an essential adjunct to lung transplantation through anterior thoracotomies.
C. Incorrect: Median sternotomy has the benefit of direct access to the ascending aorta and right atrium for central cannulation and conduct of lung transplantation on cardiopulmonary bypass. Peripheral cannulation is also feasible, but has fewer indications (e.g. calcified aorta, pericardial adhesions) in lung transplantation via median sternotomy and therefore not commonly used.
D. Incorrect: 'Clamshell' incision and central cannulation for cardiopulmonary bypass is routinely used.

Question #3

A. Incorrect: The procedure should start from the lung with the lower perfusion ratio with the anticipation that the contralateral lung will be able to support the oxygenation of the patient during the pneumonectomy and implantation of the donor lung.
B. Correct: Cardiopulmonary bypass in lung transplantation has been associated with an increase in postoperative bleeding and use of blood and blood products.
C. Incorrect: Cardiopulmonary bypass provides haemodynamic stability and control of oxygen delivery to the tissues in cases of bleeding (allowing for blood conservation with cardiotomy suction) and air leaks that can compromise conventional ventilation.
D. Incorrect: De-airing is essential in off-pump lung transplantation otherwise air bubbles can embolise to the arterial circulation.

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Anesthesia in Lung Transplantation

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Key Points

- Lungs with different pathophysiology require different ventilation strategies.
- Pulmonary hypertension is an important predictor of the use of extracorporeal support.
- Echocardiography assists in assessing right heart (dys)function and need for extracorporeal circulatory support.
- Continuous communication between the participating teams is important for a successful procedure.

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Introduction (with Definitions)

The role of the anesthesiologist is not only to focus on the anesthesia itself, but to participate in the whole perioperative process. This includes being part of the multidisciplinary team in the preoperative patient assessment, conducting anesthesia during lung transplantation (LTx) and preventing and managing intra- and extrapulmonary complications in the post-operative period. Anesthesia for patients undergoing lung transplantation must be provided with great caution since anesthetic agents may affect systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), right and left ventricular contractility, and cardiac output. Vasopressors and inotropes may be required to mitigate the effects of anesthetic agents and the hemodynamic changes secondary to surgical manipulation.

Preoperative Assessment, Investigations and Monitoring

The preoperative multidisciplinary assessment should include reviewing the indication for LTx and determining the severity of the patient's clinical condition which is indicated by the

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Lung Allocation Score (LAS). It is essential to review the patient's history of comorbidities such as cardiovascular diseases, previous thoracic surgery (e.g. pleurodesis), potential pre- and perioperative risk factors such as frailty and disability, recent infections (multi-resistant and unique bacteria), preoperative mechanical ventilation and/or extra-corporeal memberane oxygenation (ECMO) use, in order to minimize the risk of postoperative morbidity and mortality.

Pre-operative cardiovascular assessment should include a coronary angiogram, a transthoracic echocardiogram, carotid ultrasound Doppler, a right heart catheterization and a cardiac magnetic resonance imaging (MRI), in order to evaluate right and left ventricular function and the existence of pulmonary hypertension.

Detailed pulmonary assessment is necessary, such as functional status and exercise capacity and the 6-minute walking distance test (6-MWD). Furthermore, assessment of other organ systems includes evaluation of the neurological status of the patient, the coagulation status (aPTT, PT, INR) and the eventual use of anticoagulants, the liver function tests (ASAT, ALAT, total protein and albumin, fibrinogen) and the hematological status (Hb, Hematocrit, platelets, WBC count and neutrophils, blood group and antibodies). Evaluation of the renal function (urea, creatinine, and creatinine clearance) is important for the eventual use of nephrotoxic drugs and the need of a perioperative renal protection plan to reduce the severity of postoperative renal failure.

Moreover, the preoperative assessment should include all options to improve the recipient's general status such as obesity, diabetes and hypertension, optimizing the nutritional status and the preoperative pulmonary rehabilitation should be continued.

In high-risk pulmonary hypertension patients, consideration may be given to commence preoperative ECMO support to reduce the risk of primary graft dysfunction.

For intraoperative monitoring, it is advisable to include an arterial line in the right arm, peripheral oxygen saturation on the right side, ear or nose, a pulmonary artery catheter with continuous cardiac output monitoring and central venous oxygen saturation, transesophageal echocardiography, near infra-red spectroscopy (NIRS), depth of anesthesia monitor, and a bladder catheter. Additional venous lines are advisable in preparation for excessive blood loss and administration of inotropic agents. Insertion of an epidural catheter preoperatively is controversial due to the possible need for intra-operative circulatory support and heparinization.

Anesthetics

The goal of a smooth anesthetic induction is maintenance of right and left ventricular cardiac output with minimal hemodynamic disturbance. Several inotropic medications should be readily available in order to support the hemodynamics where necessary. These may be included in a checklist. Several anesthetic agents may be used during the induction of anesthesia in LTx recipients. The use of agents which may provoke the release of histamine should be avoided. Propofol is most often used in combination with an opioid, such as sufentanyl, fentanyl or remifentanil, depending on local preference. The muscle relaxant used is tailored to the patient's renal function and local practice. Positive pressure ventilation in these patients during induction may cause hemodynamic instability, most often due to air entrapment and the presence of pulmonary hypertension with or without diminished right ventricular function.

It is advisable to consider a total intravenous anesthesia technique for LTx, due to the potential inadequate uptake of inhalational anesthetics during one-lung ventilation in severely diseased lungs. If inhalational anesthetic is preferred, intraoperative end-tidal inhalational anesthetic monitoring is advisable, although the information provided may be misleading as it may not accurately reflect the concentrations in the human brain.

Hemodynamic Agents

Anesthetic agents, especially in combination with positive pressure ventilation, may cause a profound fall in the blood pressure. For this reason, medications to support the hemodynamics must be readily available at all times.

Phenylephrine (α_1), norepinephrine (α_1 and β_1) and vasopressin can all be used to increase peripheral vascular resistance. Vasopressin exerts its vasoconstrictive action via V_{1a} receptors [1] and restores vascular tone in catecholamine resistant shock by potentiating effects of adrenergic agents [1], although vasorelaxation through V_2 receptors has been described. In addition, canine models suggest that vasopressin may produce pulmonary arterial dilation via nitric oxide modulation. In pig models of hemorrhagic shock without pulmonary hypertension, vasopressin at maximum dose of 0.03 mcg/kg/min decreased PVR/SVR ratio, norepinephrine increased PVR/SVR ratio with decrease in oxygenation, and phenylephrine did not affect this ratio [2].

Inotropic support can be provided with β_1 agonists or phosphodiesterase (PDE) inhibitors. Both epinephrine (α_1, α_2, β_1 and β_2) and dobutamine (β_1 and β_2) can be used. Milrinone is a PDE inhibitor that acts as an inodilator and can cause systemic vasodilation with hypotension requiring vasopressor support. It is imperative to be prepared to start pharmacologic hemodynamic agents early to provide support during induction, especially in patients with pulmonary hypertension and impaired right ventricular function.

Ventilation Techniques Depending on Lung Disease

The application of protective ventilation strategies during LTx has an important bearing on one of the main early complications: primary graft dysfunction (PGD), which is comparable to adult respiratory distress syndrome. Protective ventilation strategies should commence with the donor and during donor lung retrieval. A randomized control trial (RCT) showed that donor lungs ventilated with tidal volumes ≤ 6 ml/kg of predicted body weight (PBW) were more suitable for transplantation than donor lungs ventilated with 10–12 ml/kg of PBW.

In recipients, protective ventilation strategies are necessary during induction of anesthesia and the transplantation procedure in order to optimize pulmonary and systemic hemodynamics [3]. Most often, a double lumen tube is used for lung separation, and its position is confirmed using fiberoptic bronchoscopy.

Certain specific lung conditions may require somewhat different approaches. In emphysematous patients, hyperinflation due to air entrapment during induction of anesthesia may lead to severe hemodynamic instability. In patients with restrictive lung disease, higher airway pressures, positive end expiratory pressure (PEEP), and relatively higher inspiratory:expiratory (I:E) ratios are commonly required. In cystic fibrosis patients, bronchial toilet through a single lumen tube is advisable before introducing a double lumen tube.

It is essential to maintain good communication between the cardiac surgeon and the anesthesiologist throughout the transplant procedure. The order in which the native lungs are deflated and transplanted should be determined at the preoperative assessment of the recipient depending on ventilation/perfusion ratios, reducing the likelihood of using extracorporeal circulatory support. Once the bronchial anastomosis is complete, fibre-optic broncoscopy is performed to inspect the bronchial suture line and for thorough bronchial toilet whilst the surgeon anastomoses the pulmonary vessels. In order to minimize reperfusion injury of the newly transplanted lung, it is advisable to carry out controlled reperfusion by slowly releasing the pulmonary artery clamp of the implanted lung. Upon reperfusion, the newly implanted lung is gently inflated using a low fraction of inspired oxygen (FiO_2) and low inflation pressures taking into consideration the donor PWB [3]. An open-lung protective ventilation strategy may be considered [4].

It is advisable to wait 20–30 minutes before the final clamping of the contralateral pulmonary artery for explanting the second recipient lung. During clamping, the entire cardiac output of the recipient is directed through the newly implanted lung and the patient becomes totally dependent on the new lung for gas exchange. At this time, problems with oxygen desaturation and/or excessive pulmonary hypertension may be signs of PGD including reperfusion edema or increased pulmonary vascular resistance due to severe vasoconstriction. Inadequate vascular anastomosis or torsion of the newly implant lung could also give rise to a similar clinical picture. Therefore, any instability on clamping of the second pulmonary artery must be communicated to the surgeon who should release the clamp and return to the newly implanted lung for a careful inspection. Although somewhat lower oxygen saturation levels are acceptable, it is sometimes necessary to use CPB or VA-ECMO in case of profound hypoxia and/or hemodynamic instability.

On completion of the LTx operation, a single lumen tube is placed using a tube exchanger before the patient leaves the operating room for the intensive care unit, unless there is severe ventilatory mismatching between the two implanted lungs.

Primary Graft Dysfunction

Primary graft dysfunction (PGD) is a form of acute lung injury that occurs within the first 72 hours after LTx. Formerly referred to as severe reperfusion injury, it is analogous to acute respiratory syndrome and presents with diffuse pulmonary infiltrates on chest X-ray due to diffuse alveolar damage resulting in impaired oxygenation and decreased lung compliance. PDG affects 11–25% of all LTx and may lead to impaired long-term graft function and increased risk of bronchiolitis obliterans. The International Society of Heart and Lung Transplantation (ISHLT) grades severity of PDG based on PaO_2/FiO_2 (P/F)-ratios in addition to radiographic infiltrates consistent with pulmonary edema. A P/F ratio less than 200 is consisted with the most severe form of lung injury and corresponds to Grade 3 PDG. Grade 3 PDG is associated with lung injury markers and worse long-term outcomes, such as 30-day mortality and overall survival.

A major perioperative limitation of LTx is failure of the allograft due to ischemic reperfusion injury involving surgical, mechanical, inflammatory and metabolic components. The principle pathophysiology is increased vascular permeability and alveolar flooding, causing the clinical symptoms of pulmonary edema, impaired gas exchange, and altered lung mechanics, such as reduced compliance/increased elastance with high distension pressures (stiff lungs).

Such lung injury can be conceptualized as a sequential series of hemodynamic, metabolic, and inflammatory insults. It starts with pulmonary manifestations of critical illness and side effects of medical management followed by brain death and the neurogenic effects of brain herniation in the donor. The sequence continues after lung retrieval with, suboptimal preservation during ischemic storage, reperfusion injury and finally, early post-implantation management.

Ischemic structural and functional damage to the microvascular endothelium and alveolar epithelium, inflammatory activation of alveolar cells, circulating and resident leukocytes, proinflammatory cytokine imbalance, and increased oxidative stress, all contribute to PGD. There is strong evidence to suggest that inflammatory genetic alterations are already present at the end of the ischemic period in lungs that subsequently suffer from PGD. Furthermore, reperfusion sets into motion programmed cell death cascades with up to 30% of lung cells exhibiting signs of apoptosis prior to chest closure.

Recipient risk factors for PGD include recipient diagnosis (e.g. sarcoidosis), obesity [5], and the presence of significant pulmonary hypertension. Donor smoking history and long ischemia time used to be considered as risk factors. However recent ISHLT data only showed such impact in combination with older donors. Moreover, there is increasing recognition that

perioperative management could influence the development of PGD.

Potentially modifiable intraoperative risk factors include single lung transplant, the recipient perioperative pulmonary arterial hypertension, use of cardiopulmonary bypass (CPB), an elevated fraction of inspired of oxygen (FiO_2), injurious mechanical ventilation, and the transfusion of large volumes of blood products [5].

Recent data has suggested that intraoperative intravenous fluid administration is a modifiable risk factor for development of PDG and ISHLT recommends cautious correction of fluid losses while optimizing hemoglobin and coagulation status of the patient [5]. Although PGD affects a significant number of LT recipients, intraoperatively it is the diagnosis of exclusion when evaluating causes of hypoxia. Accordingly, the anesthesiologist is well positioned to control these factors by limiting hydrostatic forces, preventing hyperoxia, adopting protective ventilation strategies and taking ownership of PGD (and other postoperative complications) by undertaking all efforts to control modifiable intraoperative risk factors.

The practice of controlled reperfusion and administration of antioxidants such as Vitamin C and N-acetylcysteine may also provide protection.

The recent update on the ISHLT consensus project on PGD has recommended minor changes in PGD definitions, and the mechanism and treatment review has comprehensively addressed donor, recipient, and procedure related aspects [6].

Differential Diagnosis of Intraoperative Hypoxia During Lung Transplantation

Intraoperative hypoxia shortly following lung implantation has a broad differential diagnosis. The causes of hypoxia directly related to the surgery include pulmonary vein stenosis, pulmonary arterial anastomotic obstruction, primary graft dysfunction, bronchial anastomotic obstruction and/or dehiscence, and hyperacute rejection. Other causes of hypoxia in the immediate post-transplant period include atelectasis, intra-cardiac shunt (e.g. secondary to undiagnosed patent foramen ovale), and pulmonary edema secondary to volume overload or heart failure.

Pulmonary vascular anastomotic obstruction due to stenosis, torsion or thrombosis can result in hypoxia. Vascular anastomosis can be assessed with intra-operative trans-esophageal echocardiography (TEE) after reperfusion is complete (refer to TEE findings section). Pulmonary arterial anastomosis obstruction usually presents with unexplained pulmonary hypertension not responding to therapy with possible progression to right ventricular failure and systemic hypotension. Pulmonary vein anastomosis obstruction presents with pulmonary edema on the ipsilateral side of transplantation not responsive to diuresis. Careful evaluation for presence of thrombus or air in the pulmonary veins is imperative.

Airway patency should be evaluated at the time of transplantation using a fiberoptic bronchoscope to rule out obstruction due to surgical technique or clots and secretions [7, 8].

Hyperacute allograft rejection occurs in the first 24 hours following lung transplantation, but it begins as early as minutes following allograft perfusion. It is a humoraly mediated reaction in recipients who have preformed donor specific antibodies, most commonly anti-human leukocyte antigen (HLA) antibodies [9]. Hyperacute rejection is rare nowadays due to the sensitive pre-transplant HLA screening. It presents with rapid onset hypoxemia accompanied by diffuse pulmonary edema with ground glass opacities on radiographic imaging in transplanted lung(s). Treatment focuses on removing recipient circulating antibodies and antibody producing cells as well as blocking antibodies from binding to lung epithelium [9]. This can be accomplished with plasma exchange and intravenous immunoglobulin (IVIG). Despite aggressive therapy the outcomes are poor [9].

Extracorporeal membrane oxygenation (ECMO) is often needed to support patients during the period of severe hypoxia and allow for the lungs to recover.

Types of ECMO Used

Lung transplantation is preferentially performed off pump, but cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenator (ECMO) may be used if required. Veno-venous ECMO provides respiratory support, while veno-arterial ECMO and CPB provide respiratory and hemodynamic support in cases of co-existing pulmonary hypertension or cardiac dysfunction (for more information refer to the ECMO chapter). Magouliotis et al. performed a meta-analysis comparing ECMO versus CPB and reported that ECMO was associated with better safety and short-term outcomes compared to CPB [10]. Mohite et al. also reported better early postoperative outcomes in off pump cases compared to CPB [11]. Inhalational anesthetics should be supplemented with intravenous anesthetics during veno-arterial ECMO because some of the blood flow bypasses the lungs and there is no inhalational anesthesia-delivering device incorporated into the ECMO circuit. It has been described that ECMO affects drug pharmacokinetics and therefore increases the analgesia/sedation medication requirements. Possible causes include increased volume of distribution, hemodilution and sequestration of the drug in the circuit (membrane oxygenator and polyvinyl chloride tubing [12]).

Bench studies have demonstrated significant losses of the commonly used drugs such as propofol, midazolam, morphine, fentanyl and dexmedetomidine in the circuit [13]. Bispectral index monitoring may be used in addition to clinical evaluation to adjust drug dosages and ensure the patient is adequately anesthetized. Liu et al. reported in an observational study of 20 patients undergoing LTx that closed-loop control of consciousness by titrating propofol to a BIS value of 40–60 was feasible.

Echocardiography

Transesophageal echocardiography (TEE) is an invaluable tool during LTx. It helps in diagnosing the causes and management of hypotension and hypoxia. An initial comprehensive exam may detect unexpected abnormalities that may change the course of the procedure. A significant patent foramen ovale (PFO) or heart valve abnormality may require an additional intervention and use of CPB.

Evaluation for right heart dysfunction and dilation, tricuspid regurgitation, leftward shift of the interventricular septum, and the response to pharmacologic treatment, plays an important role in determining the need for extracorporeal support. This is especially important during clamping of one of the pulmonary artery.

Although the pulmonary artery catheter is the gold standard for measuring pulmonary artery pressures [14], echocardiographic measurements may also be used to assess pulmonary pressures.

Coronary air embolism during reperfusion or injury of the left circumflex artery [15] during left pulmonary vein clamping may cause regional wall motion abnormality, which can be detected by echo. Usually these findings correlate with electrocardiographic changes. Stunned myocardium and diastolic dysfunction may occur after LTx, especially in patients with pre-existing pulmonary hypertension [16].

It is important to assess the pulmonary vessels and confirm patency and normal flow after reperfusion. A 2-D echocardiogram may reveal the presence of intraluminal masses (most likely thrombi) or stenosis due to kinking (usually with excessive artery length), suturing or external compression. Color Doppler assesses for turbulent flow and aliasing. Indications of pulmonary vein obstruction include spectral Doppler pulmonary vein peak systolic flow velocities > 100 cm/sec, pulmonary vein-left atrial peak gradient > 10–12 mmHg and diameter < 0.5 cm. High pulmonary vein velocities may be due to ipsilateral vein stenosis or contralateral artery narrowing leading to increased blood flow in the opposite lung. Contact

ultrasound may be helpful when the vascular anastomosis is difficult to visualize with TEE.

Summary and Conclusions

The anesthesiologist plays an invaluable role in LTx, both at the donor site and at the recipient site. Adequate perioperative monitoring is essential to detect abnormalities early, to allow timely interventions and to support the hemodynamic status of the recipient. Extensive experience of fiberoptic bronchoscopy and transesophageal echocardiography are essential skills during the intra-operative period.

Self-study

1. Which medication can be used for anesthesia induction during lung transplantation
   (a) Etomidate
   (b) Ketamine
   (c) Midazolam
   (d) Propofol
   (e) All of the above
2. Hypoxia after the lung implantation may be secondary to:
   (a) Acute rejection
   (b) Insufficient recruitment
   (c) Ischemia-reperfusion injury
   (d) Pulmonary vein stenosis
   (e) All of the above
3. What is an acceptable pulmonary vein velocity after lung implantation
   (a) <50 cm/sec
   (b) <100 cm/sec
   (c) >100 cm/sec
   (d) >120 cm/sec

Answers

1. (e) All of the above
2. (e) All of the above
3. (b) <100 cm/sec

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Further Reading and Related Links/ Journals/Book

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Postoperative Complications and Management

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Key Points

- Primary graft dysfunction is an early complication, defined by diffuse alveolar infiltrates and impairment of oxygenation, the most severe form might require extracorporeal membrane oxygenation support
- During the early phase after lung transplant (LTx) there is a high probability of bacterial and fungal infections with an associated high risk of morbidity
- Surveillance for multiple drug resistant bacteria should be done to avoid inappropriate empiric antibiotic treatment
- Antiviral prophylaxis should be given to all cytomegalovirus (CMV) seropositive recipients and CMV seronegative recipients who receive an organ from a seropositive donor (D+/R−)
- Acute rejection is an important risk factor for the development of chronic lung allograft dysfunction and particularly bronchiolitis obliterans syndrome.

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Introduction

Lung transplant (LTx) recipients are at risk of developing post-operative complications including primary graft dysfunction (PGD), acute rejection, opportunistic infection and chronic lung allograft dysfunction (CLAD), which probably represents chronic rejection. The management of the post-LTx process is complex and significant progress has been made in the identification, prevention and treatment of the major complications related to the lung allograft during the post-transplant phase. Immunosuppression is mandatory to prevent acute and chronic rejection of the transplanted lung. However, the compromised immune system can increase the risk of infection, especially by opportunistic agents. This chapter will describe the main postoperative complications following LTx, the mechanisms behind them and the therapeutic options.

Primary Graft Dysfunction

PGD is a form of acute lung injury that may affect lung allografts early after transplantation. This condition was defined in 2005 by the International Society for Heart and Lung Transplantation (ISHLT) [1] and was recently modified in a consensus conference in 2016 [2]. In summary, PGD is defined by the presence

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of diffuse alveolar infiltrates on chest X-ray, together with oxygenation impairment (Fig. 1). According to the working group, PGD should be graded every 24 hours from lung reperfusion, over the first 72 hours [2].

Epidemiology

Despite attempts to refine the definition of PGD, the reported incidence depends on the PGD grading system used and on the timing of the assessment [3, 4]. Before the introduction of the ISHLT definition, Christie et al. reported a PGD incidence of 10.2% in a cohort of 5,262 lung recipients [5]. Later, using the ISHLT criteria, Kreisler et al. reported a PGD incidence of 22.1% [6] worldwide. More recently, Diamond et al. reported, that 16.8% of lung recipients developed grade 3 PGD at 48 or 72 h after reperfusion in a prospective multicenter cohort of 1,255 LTx [3, 7]. The 2016 ISHLT report summarised the available literature and reported an incidence of about 30% of PGD and about 15–20% of grade 3 PGD after LTx [4].

Outcomes

The development of PGD after LTx has been associated with poorer short- and long-term clinical outcomes (Table 1). In particular, PGD has been shown to be associated with bronchial complications, reduced pulmonary function tests performance, prolonged mechanical ventilation, in-hospital and ICU length of stay and increased mortality and the development of bronchiolitis obliterans syndrome (BOS) [4].

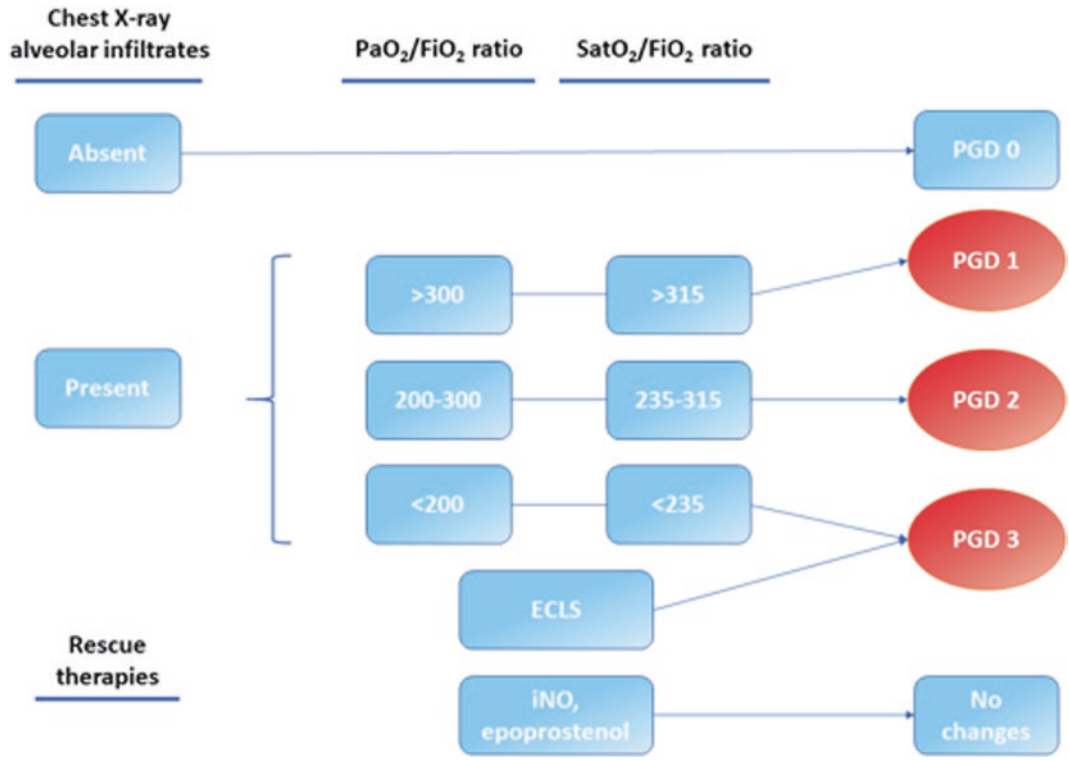

Fig. 1 ISHLT PGD definition 2016

Table 1 Impact of PGD on outcomes

Reference	PGD grade	Timing from reperfusion	Sample	Outcome	Findings
Olland et al. (2017)	All grades	0–72 h	259	Bronchial complications	PGD within 72 is a major risk factor for bronchial complications (OR = 2.55; p = 0.08)
Armstrong et al. (2016)	Grade 3	72 h	243	CPET 6MWD	No differences in CPET or 6MWD Worse HLOS and PFT
Mizota et al. (2016a)	Grade 3[a]	0 h	42	VFDs	Association of PGD3 at T0 with decreased VFDs in lobar grafts
DerHovanessian et al. (2016)	All grades	0–72 h	279	BOS	Increased rates of BOS incrementally increased with PGD severity
Ius et al. (2014)	Grade 2–3	48 h	546	DSA	Association (OR 2.6, 95% CI 1.5–4.6, p = 0.001) with early DSA development, which were independently associated with an increased risk for mortality
Diamond et al. (2013b)	Grade 3	48 or 72 h	1255	Mortality	Significant association with 90-day and 1-year mortality
Samano et al. (2012)	Grade 3	48 and 72 h	118	MV time and mortality	Higher MV time and operative and 90-day mortality in grade 3 PGD
Kreisel et al. (2011b)	All grades		1000	BOS and survival	Higher rates of BOS and impaired short- and long-term survival
Christie et al. (2010)	All grades	24–72 h	450	Survival	Grade 3 had the highest 30-day and overall mortality PGD grade at 48 and 72 hours discriminated mortality better than PGD grade at 24 hours
Huang et al. (2008)	All grades	24–72 h	334	BOS	Significant risk factor for both BOS development and progression Direct relationship between the severity of PGD and the risk of BOS development PGD grade 3 was associated with the highest risk of BOS development and progression at all time points
Daud et al. (2007)	All grades	ICU arrival	334	BOS stage 1	PGD is a significant risk factor for BOS independent of other recognized risk factors Direct relationship between the severity of PGD and the risk of BOS
Whitson et al. (2007)	Grade 3	0–48 h	374	BOS and survival	Worst score T (0–48) Grade 3 PGD negatively affects long-term survival, BOS-free survival and pulmonary function of B LTx
Prekker et al. (2007)	Grade 3	0 h	96	Mortality	P/F improvement in<20% in the first 12 h leads to a poor outcome

continued

Table 1 Continued

Reference	PGD grade	Timing from reperfusion	Sample	Outcome	Findings
Burton et al. (2007)	All grades	0–72 h	180	Mortality and various	Worse 90-day postoperative mortality and 3-year survival Higher incidence of DAD and BOOP
Prekker et al. (2006)	All grades	0–48 h	402	Mortality and survival	Worst score T (0–48) Grade 3 PGD had significantly decreased long-term survival, longer ICU and hospital stay; worst score T (0–48) and T0 Grade 3 PGD was a significant RF for short- and long-term mortality
Christie et al. (2005c)	Grade 3	0–48 h	5262	Mortality and survival	PGD is a major contributing factor to early mortality Survivors have an increased risk of death extending beyond the first post-transplant year
Thabut et al. (2002)	Grade 2–3	0–72 h	251	Mortality	Association with increased duration of mechanical ventilation and ICU mortality

[a]Lobar transplantation

List of abbreviations. *LTx* lung transplantation; *B* bilateral; *M* monolateral; *L* lobar; *CPET* cardiopulmonary exercise testing; *6MWD* 6-minute walk test; *HLOS* hospital length of stay; *PFT* pulmonary function tests; *VFDs* ventilator free days; *BOS* bronchiolitis obliterans syndrome; *DSA* donor-specific anti-HLA antibodies; *P/F* PaO_2/FiO_2 ratio; *ICU* intensive care unit; *DAD* diffuse alveolar damage; *BOOP* bronchiolitis obliterans organizing pneumonia; *MV* mechanical ventilation

Pathophysiology and Risk Factors

The 2016 ISHLT consensus statement reaffirmed the notion that PGD has no recognised aetiology, but is the result of multiple donor and recipient related factors, many of which remain unknown [2]. Ischaemia-reperfusion induced injury (IRI) of the transplanted lung is considered the major determinant of PGD and it is triggered by the activation of the inflammatory cascade [8, 9]. Vascular endothelial and alveolar epithelial homeostasis impairment and tissue macrophage, neutrophil and lymphocyte activation are considered the key actors in PGD pathophysiology [8].

Several risk factors might contribute to PGD development although the literature remains somewhat controversial. These can be broadly divided into donor or recipient related risk factors. The 2016 ISHLT report indicates that the recipient's primary lung disease, pulmonary arterial hypertension, obesity and preoperative inflammation have been associated with PGD development, as well as donor traumatic brain injury, advanced age, smoking and alcohol use. Perioperative factors such as single versus bilateral LTx, the use of cardio-pulmonary bypass, ischaemic time and the amount of blood transfusions may also influence the early graft outcome [4]. A list of studies focusing on PGD risk factors, including those about the impact of organs retrieved from donation after circulatory death (DCD) donors and of the use of ex vivo lung perfusion (EVLP) for marginal donors on PGD development, is presented in Table 2.

Treatment

The treatment strategy for PGD is to provide support therapy in order to gain time for the PGD-associated lung injury to recover and to prevent secondary organ damage. The treatment is similar to that for acute respiratory distress syndrome (ARDS): limiting fluid administration and positive fluid balance, a lung protective ventilator strategy, low haematocrit (25–30%) and optimisation of coagulation parameters [10].

Inhaled nitric oxide (iNO) can improve ventilation-perfusion mismatch and decrease the pulmonary vascular resistance (PVR) without affecting the systemic blood pressure. Some studies have shown that the use of iNO reduced the duration of mechanical ventilation (MV) [11, 12].

In severe PGD, patients who do not respond to conventional therapy and iNO might benefit from extracorporeal membrane oxygenation (ECMO) support as a bridge to recovery [12]. Veno-venous (VV) ECMO provides respiratory support and permits the use of protective lung ventilation, thus avoiding the potential harmful effects of aggressive MV [13, 14]. ECMO should ideally be used within 24 h from the diagnosis of PGD [12]. VV ECMO is generally well tolerated and is associated with fewer complications than veno-arterial (VA) ECMO providing that the patient does not require simultaneous mechanical circulatory support [15].

a. *Protective lung ventilation strategy*

Lung-protective ventilator strategies including use of a low tidal volume (V_T) improve survival in patients with ARDS [16–18]. As it has been shown that the type of damage on the lung in PGD and ARDS is similar, it follows that a similar approach could prevent or improve recovery from PGD in the LTx recipient.

Undersized allografts can lead to hyperinflation by a high V_T setting, increasing the risk of ventilator-associated lung injury.

In such patients, the vascular bed is also undersized giving risk to an increased PVR and therefore higher pulmonary artery pressure, which can result in right ventricle strain. This contributes significantly to PGD after LTx.

Therefore, the ventilator parameters should be set on estimates of the allograft size, i.e., predicted donor weight, rather than recipient weight [19].

b. *Pulmonary Vasodilators*

The development of PGD correlates with a reduction in the endogenous nitric oxide and cyclic guanosine monophosphate (cGMP) levels. Nitric oxide (NO) is a vasodilator that acts

Table 2 Acknowledged and/or potential risk factors for PGD

Reference	Year		Topic	Study design	Sample	Findings and OR (if available)
Lansink-Hartgring et al. (2018)	2018	**Donor**	Hypernatremia	Retrospective SC	474	Donor hypernatremia was not associated with grade 3 PGD at 0–72 h, MV duration, or long-term survival
Hamilton et al. (2018)	2018		Plasma PAI-1	Prospective SC	25	Recipients who developed grade 2–3 PGD had higher donor plasma levels of PAI-1
Hin et al. (2018)	2018		CCSP G38A polymorphism	Retrospective MC	104	Donor CCSP G38A polymorphism is associated with a decreased risk of grade 3 PGD (OR 0.22, 95%IC 0.041–0.88, p = 0.045)
Park et al. (2018a)	2018		Anti-HLA Ab	Retrospective SC	76	Gtade 2–3 PGD within 72 h was more frequent in patients with anti-HLA antibodies with moderate-to-high MFI values
Belhaj et al. (2017)	2017		SP-A/SP-B gene expression	Prospective SC (pilot)	13	SP-A and SP-B gene expression in the donors' lungs was reduced in grade 1/3 PGD patients
Abbas et al. (2017)	2017		TTV in BAL	Prospective SC with matched control	46	Changes in TTV levels during the perioperative period were significantly associated with grade 3 PGD within 72 h
Holley et al. (2017)	2017		Donor age	Retrospective SC	396	No interaction was seen between donor age and risk of grade 3 PGD at 72 h
Mizota et al. (2016b)	2016		Lobar LTx	Retrospective SC	75	Grade 3 PGD at 48–72 h was not different between living lobar and cadaveric LTx donors
Grimm et al. (2015)	2015		Prolonged (>6 h) graft ischemic time	Retrospective MC	10225	>6 h ischemic time was not an independent predictor of PGF (odds ratio, 1.11; 95% CI, 0.88–1.39; P = 0.37)
Eberlein et al. (2015)	2015		Lung size matching	Prospective MC	812	Oversized allografts are associated with a decreased risk of grade 3 PGD within 72 h
Somers et al. (2015)	2015		Extended donor criteria (EDC)	Retrospective SC	431	Grade 3 PGD at 12, 24 and 48 h was significantly higher in EDC recipients
Cantu et al. (2015)	2015		Oxidant stress regulatory genetic variation	Prospective MC	1038	Donor NADPH Oxidase 3 (p = 0.01) and recipient glutathione peroxidase and NRF-2 (p = 0.01) were significantly associated with grade 3 PGD within 72 h
Zych et al. (2014)	2014		Extended donor criteria (EDC)	Retrospective SC	248	After adjustment, grade 3 PGD at 72 h was more frequent in the EDC group (p = 0.046)
Baldwin et al. (2013)	2013		Donor age	Retrospective MC	8860	Marginally increased risk of grade 3 PGD at 72 h with donors age 55–64 years compared to 30–54 years (RR 1.27, 95% CI 0.99–1.63)
Moreno et al. (2013)	2013		Timing retrieval after trauma	Retrospective SC	132	PGD did not differ among donor lings retrieved within 24 h from donor lungs retrieved after 24 h of brain death

continued

Table 2 Continued

Reference	Year		Topic	Study design	Sample	Findings and OR (if available)
Alvarez et al. (2013)	2013		Gender mismatch	Retrospective SC	256	Donor–recipient gender mismatch does not have a negative impact on high grade PGD at 72 h
Diamond et al. (2013c)	2013		Clinical RF	Prospective MC	1255	Independent RF for grade 3 PGD at 48 or 72 h were history of donor smoking (OR 1.8; 95% CI 1.2–2.6; P = 0.002); FiO_2 during reperfusion (OR, 1.1 per 10% increase in FiO_2; 95% CI, 1.0–1.2; P = 0.01); single LTx (OR, 2; 95% CI, 1.2–3.3; P = 0.008); use of CPB (OR, 3.4; 95% CI, 2.2–5.3; P < 0.001); overweight (OR, 1.8; 95% CI, 1.2–2.7; P = 0.01) and obese (OR, 2.3; 95% CI, 1.3–3.9; P = 0.004) recipient BMI; preoperative sarcoidosis (OR, 2.5; 95% CI, 1.1–5.6; P = 0.03) or PAH (OR, 3.5; 95% CI, 1.6–7.7; P = 0.002); and PAPm (OR, 1.3 per 10 mm Hg increase; 95% CI, 1.1–1.5; P < 0.001)
Samano et al. (2012)	2012		Clinical RF	Retrospective SC	188	Donor smoking history was an independent RF for grade 3 PGD at 48 h (OR 4.83; 95% CI 1.236–18.896; P = 0.022) and older donors for PGD at 72 hours (OR 1.046; 95% CI 0.997–1.098; P = 0.022)
Oto et al. (2008)	2008		Heart and kidney PGD same donor	Retrospective SC	231	In multivariate analysis, same donor heart PGD (OR 3.37, 95% CI 1.19–9.50, p = 0.02) was an independent RF for grade 3 PGD at 6 h
Cottini et al. (2018)	2018	**Recipient**	PAH and others	Retrospective SC	96	Low HDL-C (OR 0.10, 95% CI 0.02–0.65, p = 0.016) but not PAH is associated with grade 3 PGD within 72 h (multivariable logistic regression)
Park et al. (2018b)	2018		CTD-ILD diagnosis	Retrospective SC	62	Incidence of PGD (all grades) within 72 h did not differ between CTD-ILD and IPF patients
Todd et al. (2017)	2017		ECMO (bridge)	Retrospective SC	93	Grade 3 PGD within 72 h was similar between patients with ECMO bridge to LTx and standard recipients
Cantu et al. (2016)	2016		TOLLIP gene	Prospective MC	728	TOLLIP gene was significantly associated with grade 3 PGD within 72 h (p = 0.006). The increased risk of PGD for carrying at least one copy of this variant was 11.7% [95% CI: 4.9%, 18.5%]
Cottini et al. (2016)	2016		Pre-Ltx dyslipidemia	Retrospective SC	264	Dyslipidemia is an intermediate risk factor for grade 3 PGD within 72 h (OR = 1.932, p = 0.049)
Porteous et al. (2016)	2016		Diastolic dysfunction	Retrospective SC	117	Higher E/e' were associated with an increased risk of grade 3 PGD at 48 h/72 h (E/e' OR = 1.93; p = 0.04; E/e' > 8 OR = 5.29; p = 0.01)
Soresi et al. (2016)	2016		Recipient pleural abnormalities	Retrospective SC	163	Pleural disease was associated with a significantly higher incidence of grade 3 PGD at 0 and 48 h (p = 0.037 and p = 0.032, respectively)

continued

Table 2 Continued

Reference	Year		Topic	Study design	Sample	Findings and OR (if available)
Geube et al. (2016)	2016		Intraoperative fluid volume	Retrospective SC	494	Each intraoperative liter of fluid increased the OR grade 3 PGD within 72 h by 22% (OR = 1.22; p < 0.001). The volume of transfused red blood cell concentrate was associated with grade 3 PGD (OR = 1.7; p = 0.002)
Kelm et al. (2016)	2016		Low muscle mass	Retrospective SC	36	No evidence of a difference in any PGD in the first 72 h by muscle index adjusted by age and sex (OR = 2.219, p = 0.32)
Pérez-Terán et al. (2016)	2016		Right ventricular function	Prospective MC	72	Better right ventricular function is a risk factor for the development of grade 3 PGD within 72 h
Cantu et al. (2015)	2015		Oxidant stress regulatory genetic variation	Prospective MC	1038	Donor NADPH Oxidase 3 (p = 0.01) and recipient glutathione peroxidase and NRF-2 (p = 0.01) were significantly associated with grade 3 PGD within 72 h
Liu et al. (2014)	2014		Various	Systematic review and metanalysis	10042	Female gender (OR 1.38, 95% CI 1.09–1.75), African American (OR 1.82, 95% CI 1.36–2.45), IPF (OR 1.78, 95% CI 1.49–2.13), sarcoidosis (OR 4.25, 95% CI 1.09–16.52), PPH (OR 3.73, 95% CI 2.16–6.46), elevated BMI (OR 1.83, 95% CI 1.26–2.64), and use of CPB (OR 2.29, 95% CI 1.43–3.65) were significantly associated with increased risk of PGD
Shah et al. (2014)	2014		Club (clara) cell secretory protein levels	Prospective MC	714	After adjustment, pre-operative CC-16 levels remained associated with grade 3 PGD at 48 or 72 h (OR: 3.03, p = 0.013) in non-IPF subjects
Diamond et al. (2012)	2012		Plasma angiopoietin-2 levels	Prospective MC	119	Angiopoietin-2 levels were significantly associated with the development of grade 3 PGD within 72 h after lung transplantation, in particular in IPF patients
Fang et al. (2011)	2011		PAPm	Prospective MC	126	Each 10-mm Hg increase in PAPm was associated with increase in odds of grade 3 PGD at 72 h (OR = 1.64; p = 0.003—unadjusted)
Lederer et al. (2011)	2011		Obesity	Prospective MC	512	Obesity was associated with a twofold increased risk of primary graft dysfunction (adjusted RR 2.1, p < 0.001). The risk of grade 3 PGD within 72 h increased by 40% for each 5 kg/m^2 increase in BMI after adjustment. Higher plasma leptin levels were associated with a greater risk of PGD (sex-adjusted P = 0.02)
Warnecke et al. (2018)	2018	**EVLP**	OCS device VS standard cold storage	Prospective non-inferiority RCT (phase 3)	320	Reduced incidence of grade 3 PGD within 72 h in the OCS group
Hashimoto et al. (2017)	2017		sVCAM in EVLP donor perfusate	Retrospective SC	100	sVCAM-1 at 1 h and at 4 h were significantly associated with grade 3 PGD within 72 h
Wallinder et al. (2016)	2016		EVLP	Prospective SC	27 (EVLP) 145	Grade 2–3 PGD at 72 h did not show any significant difference between EVLP and standard lungs

continued

Table 2 Continued

Reference	Year		Topic	Study design	Sample	Findings and OR (if available)
Terragni et al. (2016)	2016		VILI and stress index	Prospective SC	14	PGD of any grade did not differ among lungs ventilated with a protective or non-protective ventilatory setting
Boffini et al. (2014)	2014		EVLP	Prospective SC	36	PGD incidence and severity at 0 and 72 h did not show any difference between EVLP and standard lungs
Cypel et al. (2012)	2012		EVLP	Retrospective SC	317	Grade 3 PGD at 72 h did not show any significant difference between EVLP and standard lungs
Inci et al. (2018)	2018	**DCD**	DCD Maastricht III	Prospective SC	21 (DCD) 130 (DBD)	PGD grade comparable between DBD and DCD
Villavicencio et al. (2018)	2018		DCD Maastricht III	Retrospective SC	15 (DCD) 113 (DBD)	Greater incidence of grade 2–3 PGD at time 0 for the DCD group ($p = 0.001$)
Ruttens et al. (2017)	2017		DCD Maastricht III-IV-V	Retrospective SC	59 (DCD) 331 (DBD)	Grade 3 PGD within 72 h was similar in the DCD compared with the DBD group
Sabashnikov et al. (2016)	2016		DCD Maastricht III-IV	Prospective SC	60 (DCD) 242 (DBD)	Recipients from the DCD group had as higher incidence of grade 3 PGD at ICU arrival ($P = 0.014$)
Levvey et al. (2015)	2015		DCD in PAH recipients Maastricht III	Retrospective SC	11 (DCD) 20 (DBD)	Grade 3 PGD did not differ between groups
Zych et al. (2012)	2012		DCD Maastricht III	Retrospective SC	26 (DCD) 129 (DBD)	PGD grade within 72 h comparable between DBD and DCD
De Vleeschauwer et al. (2011)	2011		DCD Maastricht III	Retrospective SC	21 (DCD) 154 (DBD)	The incidence of PGD within 48 h was not different between the groups
De Oliveira et al. (2010)	2010		DCD Maastricht III	Retrospective SC	18 (DCD) 406 (DBD)	The incidence of PGD was not different between the groups

List of abbreviations. *LTx* lung transplant; *OR* odds ratio; *EVLP* ex vivo lung perfusion; *DCD* donation after circulatory death; *DBD* donation after brain death; *SC* single-center; *MC* multi-center; *RCT* randomized-controlled trial; *MV* mechanical ventilation; *PR3* proteinase 3; *NE* neutrophil elastase; *AAT* α1-anti-trypsin; *CCSP* Club Cell Secretory Protein; *IRI* ischemia-reperfusion injury; *sVCAM* soluble VCAM-1; *TTV* Torque teno viruses; *VILI* ventilator-induced lung injury; *PAH* pulmonary arterial hypertension; *CPB* cardio-pulmonary bypass; *BMI* body mass index; *PAPm* mean pulmonary artery pressure; *Ab* antibodies; *MFI* mean fluorescence intensity; *HDL-C* high density lipoprotein-cholesterol; *CTD-ILD* connective tissue disease-related interstitial lung disease; *IPF* idiopathic pulmonary fibrosis; *RBC* red blood cells

upon the vascular endothelium. Under normal conditions, NO is predominantly produced by endothelial nitric oxide synthase (eNOS) [20, 21]. Therefore, the administration of inhaled nitric oxide (iNO) during lung transplantation might be a possible method to prevent or attenuate PGD.

The administration of iNO during severe PGD might reduce pulmonary vasoconstriction, thus reducing right ventricular afterload [22] without altering systemic vascular resistance. It might also improve oxygenation by dilating the pulmonary vasculature of ventilated areas, reducing the shunt fraction and the degree of V/Q mismatch [21, 23].

However, data regarding the effectiveness of iNO in reducing time to extubation, length of intensive care and hospital stay and mortality [24] are unclear. For this reason, the routine use of prophylactic iNO in LTx cannot be recommended [21, 24, 25]. Since the effectiveness of iNO in preventing PGD is unproven, the ISHLT Working Group on PGD sum-marised that it may only have benefit in certain patient groups with established PGD.

Inhaled NO may be used in selected cases of severe hypoxemia and/or elevated pulmonary artery pressures. Extrapolating knowledge from the studies on ARDS, the beneficial effects of iNO may be real but transient. At the same time, the efficacy of inhaled prostacyclin as a pulmonary vasodilator in PGD has not been studied, but it is used in refractory hypoxia after LTx, especially when there is concomitant severe pulmonary hypertension and right heart failure[25]. A small recent study reported on the effectiveness of intraoperative inhaled iloprost in preventing PGD and preserving allograft function [26].

The administration of iNO with pentoxifylline (PTX), a methyl xanthine derivative that decreases neutrophil sequestration, might prevent PGD in lung recipients [27, 28]. It is accompanied by significant improvements in oxygenation and reductions in reperfusion-induced edema, duration of mechanical ventilation and mortality [29].

In summary, despite some positive effects from experimental and small observational studies, the use of iNO after LTx has no significant effect on oxygenation or on PGD prevention in randomised clinical trials [30–32].

c. *Extracorporeal membrane oxygenation*

ECMO can be used to provide cardiorespiratory support in patients with refractory hypoxaemia or right ventricular failure caused by severe PGD and it might help in applying lung protective ventilation strategies [33]. It is reported that ECMO is used in 2–9% of patients undergoing lung transplantation [34–37, 38].

Mortality rates vary between 30 and 60%, depending on the patient's characteristics, time of ECMO duration, coexisting infection or rejection, and the type of ECMO support (VV vs. VA) [34, 35, 39–42].

In adult lung transplantation, only a few studies reported on the effectiveness of ECMO for treatment of PGD and data on long-term survival are still lacking [43].

The success of ECMO support after LTx is primarily influenced by the reversibility of allograft dysfunction rather than by the type of support used. VA ECMO may improve both oxygenation and haemodynamic and potentially limit the ischaemic-reperfusion response from decreasing the pulmonary artery pressure, but requires higher anticoagulation levels may increase the risk of hemorrhagic and neurologic complications. VV ECMO is associated with less vascular complications and often lower anticoagulation requirements [14] and is hence the preferred mode of support for PGD unless there is severe, concomitant ventricular dysfunction or hemodynamic impairment.

Moreover, since the bronchial arteries are not routinely revascularized at LTx, the use of VA ECMO could worsen parenchymal ischaemia by limiting pulmonary arterial blood flow, while VV ECMO offers the controlled flow of oxygenated blood through the lung parenchyma, minimising the hypoxic pulmonary vasoconstrictive response and the risk of distal pulmonary vasculature thrombosis.

Allograft recovery from PGD usually occurs within 7–10 days of ECMO support and successful weaning after a period longer than 14 days is uncommon. Therefore, the futility of support longer than 14 days must be considered in patients with PGD unless re-transplantation is considered.

The main causes of early mortality in these patients are infections and permanent graft failure.

In conclusion, the use of ECMO for PGD after LTx is associated with acceptable survival and complication rates [33].

Cannulation Strategies

Cannulation for VV-ECMO usually involves the direct cannulation of two central veins: drainage of deoxygenated blood from the inferior vena cava (IVC) via the femoral vein and reinfusion of oxygenated blood into the superior vena cava (SVC) and right atrium via the internal jugular vein or femoral vein [44]. This approach might be performed at the bedside without the need for imaging guidance. However, femoral cannulation compared to jugular one tends to limit the patient's ability to ambulate [45]. The possibility of placing a bicaval, dual-lumen cannula via a single internal jugular allowing for both drainage and reinfusion has certain attractions [46]. The use of fluoroscopy or transoesophageal echocardiography is recommended during cannulation to ensure safe and correct cannula placement and orientation [47]. VV ECMO can usually be instituted in awake patients and indeed there are benefits of remaining free from sedation and mechanical ventilation if this is possible. For patients requiring ECMO support for the management of PGD, especially if the duration of ECMO support is estimated to be short-term, a two-site VV configuration is more practical.

For transplant candidates with concomitant cardiac impairment, VA ECMO support may be necessary [48]. This scenario is most commonly encountered in patients with pulmonary arterial hypertension and right ventricular dysfunction, with or without diffuse parenchymal lung disease [49–51]. Traditionally, VA ECMO involves femoral venous drainage and femoral arterial reinfusion, which poses a significant limitation to mobilisation. Importantly this configuration may be inadequate for upper-body oxygenation if there is impaired native gas exchange and sufficient residual native left ventricular output such that the ascending aorta and aortic arch are supplied with relatively deoxygenated blood (Harlequin syndrome) [48, 52]. Patients at risk of Harlequin syndrome should be monitored carefully and upper body saturation monitoring used (e.g. right arm pulse oximetry, cerebral oximetry).

The addition of a reinfusion cannula into the internal jugular vein via a Y-connection off the arterial reinfusion limb, creating a veno-arterial venous circuit, may provide better upper-body oxygenation [52].

Retransplantation

Re-transplantation raises many of the same considerations as the initial transplantation, with higher incidence of complications such as PGD, rejection, and infection [53]. The most common reasons for re-transplantation are BOS (63%), PGD (15%), and acute rejection (4%) [17].

Airway Complications

Airway complications occur in up to a third of patients after LTx and result in significant morbidities and mortality (2–4%) [54]. Airway complications may become apparent acutely in the early postoperative period or develop days or weeks later. The development of airway complications after LTx can add significant limitations to the patient's quality of life because of respiratory symptoms and functional impairment, the need for regular follow up, bronchoscopic surveillance, additional medications and interventions [54–56].

Airway complications may occur around the bronchial anastomoses or distal airways and include stenosis, infection, bronchopleural

fistula, formation of excess endobronchial granulation tissue, ischaemia, necrosis, dehiscence and bronchomalacia. The main cause of airway complications is ischaemia of the donor bronchi. After the normal anatomical bronchial arterial blood supply has been severed at the time of donor lung procurement, the newly transplanted lung becomes dependent on retrograde blood flow from the pulmonary arteries until revascularization occurs some weeks later. Airway complications are more likely in recipients with chronic infections such as cystic fibrosis, hence the need to aggressively treat suspected postoperative infections in these patients. Surgical technique is an important factor in the development of airway complications and bronchial anastomotic techniques have been refined to preserve bronchial blood supply [54, 55, 57].

Bronchial stenosis is the commonest airway complication affecting around 15% of LTx recipients, occurring either at the anastomosis or distal to it. This usually becomes apparent after 2–3 months and can result in significant morbidity and mortality. The main causes include ischaemia, infection and rejection. Diagnosis is made from bronchoscopy, spirometry and CT scan [55].

Dehiscence of the bronchial anastomosis is a serious complication with a high mortality. It is suspected in patients with persistent air leak, pneumothorax or sepsis, or simply observed on routine bronchoscopy. Ischaemia is the most likely cause but the use of drugs that inhibit the mammalian target of Rapamycin (mTOR inhibitors) such as sirolimus may contribute to this [55].

Bronchomalacia leads to dynamic airway collapse and obstruction. It is usually seen within four months after LTx and patients typically present with dyspnoea, cough, an obstructive defect on spirometry and recurrent infections. Bronchoscopy remains the gold standard for diagnosis [54, 55].

Suspected or proven airway complication necessitates frequent bronchoscopic surveillance. Potential interventions include bronchial toilet and clearance of secretions, dilatation, stent insertion, ablation e.g. cryotherapy and surgery including reconstructing the anastomosis or re-transplant [55, 57].

Infections are commonly associated with airway complications and may increase morbidity and mortality. Prophylactic antibacterial and antifungal agents are hence commonly used [54].

Pleural Complications

Chest drains are routinely placed at the time of LTx and typically removed within seven days. Pleural effusion occurs commonly and in around a quarter of LTx recipients as the result of increased alveolar permeability, pleural inflammation, postoperative atelectasis and impairment of lymphatic drainage. Most of these are non-infective. The effusion fluid is usually exudative; an elevated LDH and neutrophil count in the fluid are markers of infection [58].

Neurological Complications

Neurological complications after LTx are observed in 50–70% of patients. The central (CNS), peripheral (PNS) or autonomic (ANS) nervous systems can all be affected. The most common complications affecting the CNS are cerebrovascular accidents (ischaemic or haemorrhagic stroke) and encephalopathy, with age being the most important risk factor. Encephalopathy or impairment of consciousness may be due to hypoxia, metabolic derangements, immunosuppressant drug toxicity and sepsis. Neurotoxicity is mainly due to calcineurin inhibitors and can manifest as confusion, tremor, paraesthesia, blindness, seizures and encephalopathy. Changing cyclosporine for tacrolimus often improves symptoms of neurotoxicity [59, 60].

Within the PNS, neuromuscular complications may affect single or multiple nerves, plexuses or muscles. Neuropathies includes phrenic nerve and recurrent laryngeal nerve injuries presumably arising from surgery or compression injuries (deep peroneal, brachial plexus).

Phrenic nerve injury and subsequent diaphragmatic palsy may present as a patient slow to wean from mechanical ventilation. This can be demonstrated on chest ultrasound. Treatment is conservative but diaphragmatic plication is an option in persistent cases [60].

The most common complication of the PNS is critical illness polyneuropathy/myopathy. It occurs in 30–40% of patients and it is characterized by profound limb weakness and difficulty in weaning from mechanical ventilation. These patients have a longer ICU and hospital stays and are therefore more susceptibility to infections and other complications [60]. Gastroparesis is the most common ANS complication, as result of surgical damage to the vagus nerve at the time of surgery, although gastroparesis after lung transplant is often multifactorial in aetiology and not solely limited to vagal injury [61].

Gastrointestinal Complications

Gastroparesis leads to delayed gastric emptying, gastro-oesophageal reflux, aspiration and a delayed return to normal oral intake. Gastro-oesophageal reflux disease (GORD) and chronic aspiration is associated with allograft injury, functional decline, and acute and chronic rejections. Long-term gastrointestinal complications are commonly associated with higher doses of immunosuppression, manifesting as nausea, vomiting, GORD and abdominal pain[61, 62].

Anti-reflux surgery is safe in selected LTx recipients and can improve lung function and survival [63].

Cardiovascular Complications

Atrial Arrhythmias

Atrial arrhythmias occur in 30% of LTx patients and atrial fibrillation (AF) is the most common, occurring within the first two to seven days [64]. The aetiology is unclear but is perhaps linked to changes in the left atrium that occur during LTx surgery. The main risk factors for the development of AF after LTx include advanced age, idiopathic pulmonary fibrosis, coronary artery disease, diastolic dysfunction, left atrial enlargement and the use of vasopressors. Patients who develop arrhythmias have a longer postoperative stay and a higher mortality. Furthermore, postoperative pain, fluid shifts and use of vasopressor or inotropic agents can exacerbate or precipitate arrhythmias, so should be managed carefully in these patients [64, 65]. Rate control should be the priority and anticoagulation should be considered if the arrhythmia persists over 24 hours. The use of amiodarone should be limited owing to its implications in lung injury and amiodarone has been shown to significantly increase mortality in LTx recipients.

Right Ventricular Dysfunction

Patients with significant preexisting cardiovascular disease are generally excluded from LTx. However, right ventricular (RV) dysfunction is commonly associated with chronic lung diseases, especially those with pulmonary hypertension due to pulmonary vascular disease [66]. The thin-walled RV is prone to dysfunction due to its inability to tolerate abrupt increases in afterload (pressure) or preload (volume). RV failure is uncommon but may occur as the result of increased afterload, excessive volume or reduced contractility. Many of these factors can also affect left ventricular (LV) function although LV dysfunction is often the result of RV dysfunction, perhaps through ventricular interdependence when there is a leftwards shifting of the interventricular septum [67]. Single lung ventilation, which may be required to perform LTx, especially prior to implantation of the first donor lung, may worsen RV function by deleterious effects on pulmonary vascular resistance (hypoxia, hypercarbia, respiratory acidosis) and increases in intrathoracic pressure. Studies have shown that RV size, strain, function and pulmonary artery (PA) pressures usually improve after LTx, due to reduction of RV afterload and subsequent reverse remodelling. Thus, postoperative RV dysfunction and elevated PA pressures are predictors of mortality. A group of patients particularly at risk of acute heart failure after LTx are those with pulmonary arterial

hypertension (PAH), e.g. idiopathic or primary pulmonary hypertension [66]. These patients are challenging to manage and their survival is amongst the lowest of all LTx recipients. PAH is also one of the most significant recipient-related risk factors for developing PGD. Following LTx, there is a sudden normalisation of pulmonary vascular resistance and reduction in RV afterload, with an immediate increase in cardiac output and LV filling, which may unmask LV failure. Another mechanism of LV dysfunction is through ventricular interdependence in cases of acute RV failure post operatively, as such these patients need to be carefully managed in centres with expertise, using inotropic agents and often ECMO pre- and post-surgery to mitigate the sudden physiological changes on both ventricles.

Renal Complications

Acute kidney injury (AKI) occurs in 25–60% of LTx recipients when using either R-(risk), I-(injury) or F-(failure) criteria from the RIFLE definition. The aetiology may be related to lung 'biotrauma' affecting the kidneys, the inflammatory response, hypoperfusion and nephrotoxic drugs (excess diuretics, immunosuppressants and antibiotics). Renal dysfunction from calcineurin inhibitors is the most common long-term complication encountered in LTx recipients. Management involves adding angiotensin converting enzyme inhibitors, reducing doses of calcineurin inhibitors and avoiding nephrotoxic levels, or replacing them with alternatives such as the mTOR inhibitors such as sirolimus or everolimus and/or the anti-proliferative mycofenolate mofetil [68].

Identifiable risk factors for the development of kidney injury include poor preoperative renal function, a diagnosis of idiopathic pulmonary fibrosis or primary pulmonary hypertension, the need for ventilatory or ECMO support preoperatively, and bilateral lung transplantation. 'Prerenal' hypoperfusion appears to be the most significant risk factor as seen in those patients with peri-operative haemodynamic instability and requirement for high doses of vasopressors [69, 70]. Around 5–15% of patients with AKI will require dialysis and those with severe AKI (RIFLE-F) have increased length of stay and mechanical ventilation and increased mortality. At one year after LTx, the incidence of severe renal dysfunction (creatinine > 2.5 mg/L) or requiring chronic dialysis is around 5%. This goes up to 25% at ten years. Management involves identifying at-risk patients, supportive care (judicious use of fluids and vasoactive drugs, management of heart failure and avoiding further insults such as nephrotoxic drugs).

Infections

Infections are frequent complications in patients recovering from LTx, accounting for 20–25% of all post-transplant death during the first year. More than two thirds of infectious complications affect the respiratory tract [71–73].

The risk of infection in LTx is related to recipient factors and the type of transplant and severity and progression by the infecting microorganism and the state of immunosuppression.

In assessing a patient for a possible LTx, it is essential to investigate for former infectious diseases with a panel of serological tests including cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis B (HBV) and C viruses, herpes simplex virus (HSV), human immunodeficiency virus (HIV), *Treponema pallidum* and varicella-zoster virus (VZV). It is also important to perform bronchoalveolar lavage to document the bronchial flora. In case of methicillin-resistant *Staphylococcus aureus* (MRSA) carriers, some groups suggest an eradication protocol for the upper and lower respiratory tract [74].

At the time of listing, history of possible tuberculosis (TB) should be carefully investigated. In case of active TB, proper therapy should be completed. Tuberculin skin testing and/or QuantiFERON Gold TB test is recommended in all patients [75].

Transplant centres should follow the national vaccination program prior to lung transplantation. HBV, pneumococcal and meningococcal vaccinations should be implemented,

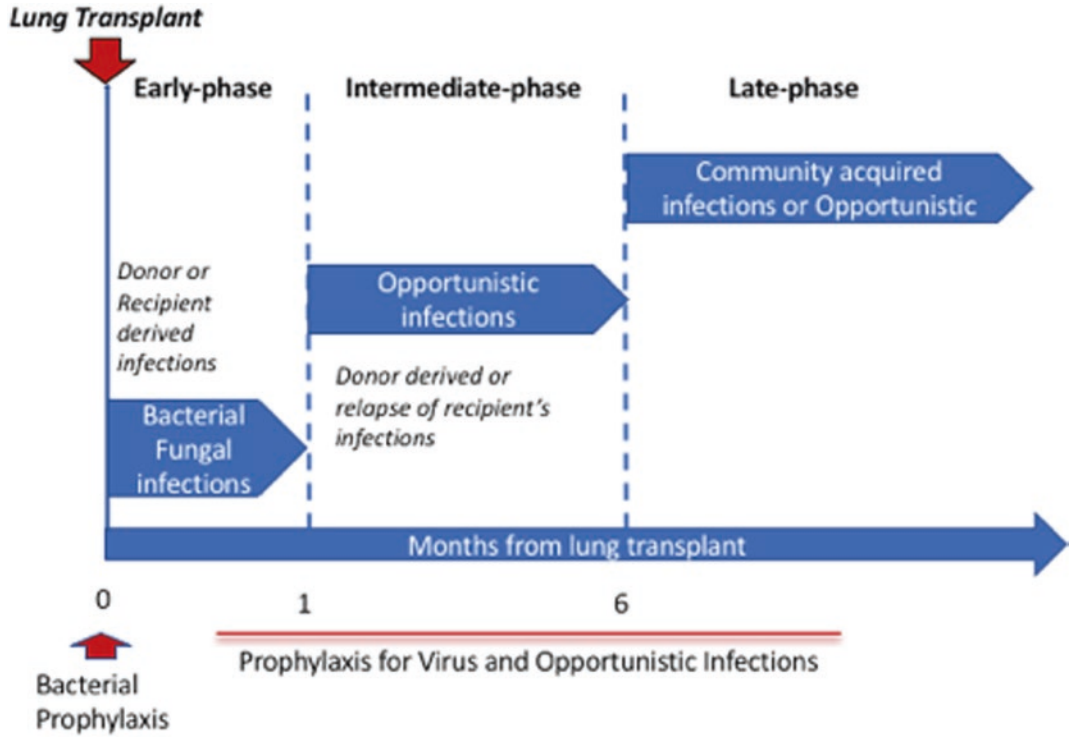

Fig. 2 Risk of infection during the different phases in the post-transplant period

considering that a time lapse of at least 3 months is advisable between vaccination and transplantation[76]. Before and after transplantation, influenza vaccination is highly recommended for both patients and close family members [75].

Post-transplant infections can be divided in donor-derived or recipient-derived. Lung recipients might have an increased risk of developing infections in the post-transplant period because of the requirement for immunosuppression, the adverse effects of transplantation on local pulmonary host defence, a constant contact with the environmental system or colonisation due to prolonged exposure to broad-spectrum antibiotics for frequent infections, such as in cystic fibrosis (Fig. 2).

Recipient Derived Infections

The recipient's pre-transplantation clinical status is essential; patients with renal failure, with advanced age, on mechanical ventilation, or with impaired nutritional status (both with obesity or malnutrition) have a higher incidence of infection after LTx [77].

Underlying chronic diseases, such as diabetes mellitus, may also be relevant to the type and severity of infections. Currently, most programs accept MV as a bridge to LTx for patients previously included on the waiting-list [78]. However, pre-transplant MV is a risk factor for nosocomial infection and prolonged postoperative ventilatory support.

Various treatments administered to candidates before LTx, especially corticosteroids or antimicrobials are associated with a higher incidence of bacterial and fungal infection in the immediate post-transplantation period.

Some risk factors are related to the transplant surgery and the type of technique used. The duration of ischaemia after donor lung extraction, the reimplantation without re-establishment of the graft's lymphatic drainage and

innervation may all affect the graft's defense mechanisms, as these may paralyse the mucociliary clearance of the airway. The graft denervation and the airway anastomosis compromise the cough reflex, hindering the control of secretions. A small inoculum of microorganisms from the graft can cause severe pneumonia in the already immunosuppressed recipient, as does constant contact with ubiquitous airborne virus and bacteria.

Patients with BOS are usually heavily immunosuppressed and have mucociliary dysfunction and are more prone to serious infections, which is the leading cause of death in this population.

Donor Derived Infection

Almost all potential lung donors harbor pathogenic microorganisms at the time of procurement, with important considerations on donor selection and on the choice of prophylactic antibiotics for the recipients [79].

A bronchial microbiological sampling, aspiration or washing, to carry out Gram and Ziehl-Neelsen staining and specific cultures for bacteria, fungi and mycobacteria, should be routinely performed in the lung donor so as to choose the appropriate recipient antibiotic prophylaxis. To avoid a long delay in results new technologies may play a role; such as rapid diagnostic tools, PCR assays for serum, swabs, bronchoalveolar lavage and other fluids.

Although the presence of a positive Gram stain or scanty purulent secretions should not be a contraindication for accepting a donor lung, some groups consider the presence of pneumonia, abundant and persistent purulent secretions or the growth of filamentous fungi an important risk factor for the development of subsequent infections and, in selected cases, a contraindication to lung acceptance. The role of prophylactic or even pre-emptive antimicrobial therapy is not clearly demonstrated and advice from infectious diseases specialists experienced in lung transplant may be required [80].

Antimicrobial Prophylaxis

The general trend for antibacterial prophylaxis in solid organ transplantation is one of a short duration of treatment primarily aimed at the skin flora, to prevent surgical site infections [81, 82].

Few well-design, prospective, comparative studies of antimicrobial prophylaxis have been conducted with patients undergoing solid organ transplantation, and no formal recommendations are available from expert consensus panels or professional organisations [83–85].

No formal studies have shown the optimal prophylaxis for patients undergoing LTx and reports are generally retrospective, single-centre studies using a variety of agents and treatment durations. Most centres maintain antimicrobial prophylaxis up to 7 days after transplantation or at least until drainage removal [86].

Multi-drug Resistant (MDR) Organisms

Multidrug-resistant (MDR) and especially carbapenem-resistant gram negative (GN) bacteria are spreading at an alarming rate. These organisms are increasingly recognised as cause of severe infections in transplant recipients [87].

In a recent Italian study on 887 transplant recipients, the incidence of carbapenem-resistant gram-negative (CR-GN) isolates was found to be 2.39 per 1000 recipient-days. In those with positive cultures for gram negative bacteria within three months after transplantation, 26.5% were CR-GNs. Carbapenems resistance was particularly frequent among Klebsiella spp. isolates (49.1%). The isolation of GN bacteria was most frequent among recipients with a longer hospital stay, lung recipients and those admitted to hospital for more than 48 h before transplantation. Recipients with CR-GM isolates had a 10.23-fold increase in mortality rate [88].

Another study reported that the length of ICU stay and previous exposure to broad-spectrum antibiotics were associated with an increased risk of emergence of MDR bacteria [85].

Donor colonisation does not represent a contraindication to transplantation, although actively infected lung grafts should be avoided. It is, however, associated with an increased risk of infection. Recipient colonisation is not a contraindication to transplantation although these patients are at increased risk of infection post-transplant. Patients colonised with CR-GN bacteria do not require different surgical prophylaxis regimens. Timely detection of carriers and contact isolation, as well as antibiotic control policies are fundamental preventive measures [89].

Colonised recipients should receive empirical treatment, better called pre-emptive, since the antimicrobial therapy may be adjusted on susceptibility study results as well as based on the severity of infection. In selected cases of colonisation, and specifically in case of *P. aeruginosa*, lung transplant recipients may benefit from prophylactic inhaled antibiotics [89].

Recipient colonisation with *ESBL-producing Enterobacteriaceae* is associated with worse outcome, but it is not a contraindication for transplantation. In case of infection, empirical treatment should avoid the use of carbapenems. Currently, there is no evidence that decolonisation of lung recipients confers benefits [87, 89].

Respiratory tract colonisation by MDR *P. aeruginosa* is especially common in patients with cystic fibrosis, with a prevalence of >50% that may increase to 75% after transplantation. *P. aeruginosa* is also the leading cause of hospital-acquired pneumonia after lung transplantation, accounting for up to 25% of cases [90]. *Acinetobacter baumannii* infections are commonly associated with epidemic outbreaks, causing more commonly hospital or ventilator-acquired pneumonia, but also urinary tract infections, catheter-related bloodstream infections and surgical site infections. All the infectious complications caused by *A. baumannii* involve a high mortality rate [90, 91]. Moreover, *Burkholderia* spp. has been related to various complications after LTx, such as chronic lung infections, mediastinal abscesses, mediastinitis, pleural effusion or chest wall infection[92]. *Clostridium difficile* causes over 70% of antibiotic-associated colitis, and over 90% of antibiotic-associated pseudomembranous colitis, with an estimated incidence of 7–31% [93, 94]. Risk factors for *C. difficile* are prolonged ICU and hospital stays, intense immunosuppression and exposure to broad-spectrum antimicrobial agents. Presentation after LTx may be atypical, with little diarrhoea. Abdomen CT scan may be useful to rule out pseudomembranous colitis, burdened by a high risk of bowel perforation. Treatment options specific for organ transplant recipient have recently been issued and include oral metronidazole in the absence of severe complications or a combination of intravenous metronidazole and oral vancomycin in complicated cases [95].

Fungal Infection

Lung transplant recipients have a high risk of fungal infections, especially from *Aspergillus spp*. Other fungi that can cause severe infections in this population are *Cryptococcus*, *Fusarium*, *Scedosporium*, *Mucor* and endemic agents (*Blastomyces*, *Coccidioides* and *Histoplasma*). *Pneumocystis jirovecii* is a unicellular fungus that may cause severe disease in immunocompromised hosts, including LTx patients. Lifelong prophylaxis with trimethoprim-sulfamethoxazole is highly recommended.

Invasive aspergillosis (IA) is one of the most hazardous infectious complications after LTx that usually occurs within one year after transplantation. Bronchial anastomotic infections with aspergillus commonly occur within the first three months after LTx and may evolve towards an ulcerative tracheobronchitis [96].

There is significant controversy regarding fungal infections in LTx and wide variation in practice regarding prophylaxis and treatment among centres. In general, the risk of invasive candidiasis is low amongst transplant recipients but IA remains a significant problem with a high mortality [96, 97].

With the introduction of inhaled Amphotericin B (Amph-B), there has been a dramatic reduction in the incidence of invasive candida infections since the 1980s. Moreover,

the survival rate of those patients who developed and those who did not develop invasive candida infections is similar [98].

A recent world-wide survey showed that thirty-four centres of fifty-eight involved in the study (58.6%) administered universal antifungal prophylaxis within the first six months after transplantation[99]. This was primarily directed against *Aspergillus species* in nearly all centres. The most common antifungal prophylaxis was voriconazole for up to three months after lung transplant as monotherapy, followed by itraconazole and inhaled Amph-B. Others centres preferred a combination therapy for prophylaxis within the first six months after transplant and the majority chose the combination of voriconazole and inhaled Amph-B. Half of the centres discontinued antifungal prophylaxis after six months.

A recent systematic review and meta-analysis of 22 reports showed that there was no significant reduction in invasive aspergillosis (IA) between patients that received universal anti-fungal prophylaxis and those ones that did not received prophylaxis [100, 101]. However, inhaled lipid preparation of Amph-B appeared to be significantly superior to no prophylaxis. While many studies addressed the clinical effectiveness of inhaled Amph-B in preventing IA in LTx recipients, with different formulations and dose of administration, only one study evaluated the intrapulmonary disposition of Amph-B after aerosolised delivery of the lipid preparation: daily administration of 1 mg/kg of inhaled Amph-B lipid complex for 4 consecutive days, followed by a weekly administration achieved Amph-B concentration in epithelial lining fluid above minimum inhibitory concentration (MIC) for *Aspergillus* [102–104]. If systemic antifungal prophylaxis or treatment with azoles is needed, therapeutic drug monitoring should be integrated in the post LTx follow up to reduce the risk of sub-therapeutic azole plasma trough levels in patients with cystic, and toxicity in patients older than 65 years [105, 106].

In conclusion, antifungal prophylaxis should be considered to reduce the risk of IA. A lipid formulation of Amph-B is preferred with aerosolised administration, to minimise the side effects. Routine prophylaxis with intravenous fluconazole for *Candida* should be discouraged, to avoid the risk of resistance or the selection of *non-albicans* species. Mucormycosis accounts for approximately 2% of all invasive fungal infections in transplant recipients. Diabetes, renal impairment and recent rejection represent risk factors. Mucormycosis is characterised by invasion of the vasculature by fungal hyphae that cause infarction and necrosis of host tissues. Pulmonary disease manifestations, such as consolidation, nodules and cavities, are the most frequent presentation in LTx recipients, even if cutaneous, sino-orbital, and disseminated disease have been reported. Histopathology and culture are both necessary for the diagnosis. Mucormycosis has an overall mortality ranging from 49 to 90%. Immunosuppression reduction and intravenous lipid Amph-B are the cornerstone of therapy, together with surgical debridement and a subsequent change to oral posaconazole if stabilisation is achieved [100].

Viral Infections

Cytomegalovirus (CMV) is the most common viral infection in solid organ transplantation and represents the major cause of morbidity and mortality during the first six months after LTx. The incidence of symptomatic CMV disease ranges from 30 to 50% with the highest incidence and severity among LTx recipients. The greatest risk of CMV infection is in seronegative recipients who receive an organ from a seropositive donor (D+/R−) and in seropositive recipients, independently from the donor (D+/R+or D−/R+). Beyond pneumonitis, CMV has been associated with numerous indirect effects including an increased risk of opportunistic infections via immune suppression by CMV itself and increased risk of acute and chronic rejections [107–111]. When pre-transplant serology of the recipient is negative, re-testing at the time of transplant is mandatory. If the pre-transplant serology is equivocal in the donor, assume

it is positive. Prophylaxis should be administered in seronegative recipients who receive an organ from a seropositive donor (D+/R−) and in seropositive recipients, independently from the donor. Both antigen levels and viral load tests are acceptable options for diagnosis, decisions regarding pre-emptive therapy, and monitoring response to therapy. A large Cochrane systematic review on CMV prophylaxis has provided high quality evidence for antiviral prophylaxis when compared to placebo or no treatment for preventing CMV disease and for reducing mortality associated with CMV disease in solid organ transplants [107]. Ganciclovir, and more recently valganciclovir, have been recognised as the drugs of choice for both prevention and treatment of CMV in transplant recipients. Currently, several preventative strategies exist to reduce the incidence of CMV disease. Some practitioners endorse universal prophylaxis, whereas others promote pre-emptive therapy (viral monitoring with early treatment) [107, 110]. The optimal duration of antiviral prophylaxis is unknown. A multicentre randomised trial showed that extending prophylaxis with Valganciclovir from three months to 12 months significantly reduced CMV infection, CMV disease and disease severity without increased ganciclovir resistance or toxicity [112]. In addition, prophylaxis with CMV immunoglobulin combined with antiviral prophylaxis might offer an advantage [113–118].

Other Viruses

Community acquired respiratory viruses (CARV) include influenza, parainfluenza, rhinovirus, adenovirus, respiratory syncytial virus, and coronaviruses. All these infections are of concern in LTx recipients and potentially increase the risk of lung allograft dysfunction [119].

The incidence of CARV varies between 7.7 and 64% and is largely dependent on the diagnostic techniques used and seasonal variation [120–122]. For most viral infections, no specific therapy is available and management is supportive. For those viruses in which treatment options are available (e.g. oseltamivir and zanamivir for influenza, ribavirin for paramyxovirus family), timely initiation is essential to limit complications [123, 124].

Recent evidence indicates that approximately 10% of LTx recipients present with Epstein Barr virus (EBV) mismatch (D+/R−). Acute EBV infection causes a polyclonal expansion of B cells hosting the virus [125]. In immunosuppressed LTx recipients, the latently infected B cells could cause post-transplant lymphoproliferative disorders (PTLD). Routine monitoring of blood specimens from transplanted patients to track EBV viral load may provide early detection of possible PTLD [126].

The rate of PTLD in LTx recipients ranges between 5 and 15% [127].

Although not supported by evidence-based medicine, some transplant centres use prophylactic antiviral treatment consisting of acyclovir or ganciclovir in high-risk patients for primary EBV infection following surgery (EBV D+/R−).

In the case of *Varicella Zoster Virus* (VZV), pre-transplant evaluation of recipient VZV immune status is highly advisable, as well as vaccination of non-immune recipients. Reactivation of VZV in LTx recipients typically occurs later than CMV or HSV. Cutaneous lesions may be delayed or atypical with haemorrhage. In LTx recipients, there is an increased risk of severe VZV complications, such as cutaneous dissemination and visceral end organ involvement (pneumonia, hepatitis, encephalitis) [128].

Mycobacteria

Amongst the differential diagnoses in LTx recipients with infection, Mycobacterial infections must be considered, including both Mycobacterium tuberculosis (MTB) and non-tuberculous mycobacteria (NTM). All mycobacterial infections are difficult to diagnose due to their prolonged culture requirements, and the complexity of multi-pharmacological treatment regimens, especially in the context of antimicrobial resistance. All solid organ transplants are at an increased risk of

post-transplant TB with a highest risk in LTx recipients, with reported incidence ranging from 6.4 to 10%, [129, 130].

Over 90% of TB cases develop within the first year following transplantation, and roughly three quarters involve the lungs [131]. Clinical presentation of active TB involves systemic symptoms and signs in association with respiratory symptoms, as the lung is the most commonly involved site. Diagnosis is challenging because of traditional time-consuming microbiological culture, but the recent introduction of nucleic amplification tests may provide rapid results and differentiation between MTB and NTM species. Treatment for LTx recipients with active TB is the same as for immunocompetent patients. However, it must be considered that the number of drugs used, the length of treatment, the drug induced toxicity and the risk of drug interactions is more complex in LTx recipients [132].

Acute Rejection

Despite advances in immunosuppression, acute allograft rejection remains a common complication in the first year after LTx and its incidence is highest in the first six months. Rejection can be hyperacute (occurring within minutes after the vascular anastomosis), acute (days to weeks after transplantation), late-acute (occurring three months after transplantation), or chronic (months to years after transplantation). Rejection is classified according with the pathophysiologic process as acute cellular rejection (ACR) or antibody-mediated rejection (AMR) [133].

Acute rejection may affect the vasculature and the small airways of the lung allograft and manifest as ACR, involving small vessels, or lymphocytic bronchiolitis (LB) involving the small airways. According to the ISHLT registry report, almost 30% of LTx recipients have at least one episode of ACR in their first year after transplantation, which may be an underestimate. Acute rejection is an important risk factor for the development of CLAD and particularly BOS[133–135].

Induction therapy is an intense immunosuppressive therapy administered at the time of LTx with the aim of reducing early acute rejection. Patients with acute rejection present with non-specific respiratory symptoms including cough, dyspnoea, sputum production and low-grade pyrexia which may be difficult to differentiate from infection or other complications. Spirometry and imaging (CXR or CT) are not very sensitive or specific and transbronchial lung biopsy remains the gold standard for the diagnosis of acute rejection. Pulse-dose corticosteroids are the cornerstone of therapy for ACR. Mild rejection (which is usually not associated with clinical signs or symptoms of allograft dysfunction) is the threshold for most centers to start therapy with bolus methylprednisolone (10–15 mg/kg daily for three days). Augmented immunosuppression can improve graft function, lessen lung injury and protect from future acute rejection episodes [133, 135].

AMR is mediated by the presence of donor-specific antibodies (DSA). The antigen–antibody complex results in an amplified immune response leading to histopathological changes to the graft and subsequent dysfunction to a variable degree. AMR may occur in either a pre-sensitized patient during the early post-transplant period, or after the emergence of de novo DSAs in the late post-transplant period, typically after inadequate immunosuppression. Clinical AMR is associated with measurable allograft dysfunction, which can be asymptomatic. AMR may also be sub-clinical, with histological changes seen but normal allograft function. Hyperacute rejection is now extremely unlikely after LTx because screening for preformed antihuman leukocyte antigen (HLA) antibodies is very sensitive. A less severe form of AMR occurring weeks or months after transplantation has been reported [133].

Treatment includes depletion of circulating antibodies, suppressing B-cells to mitigate further antibody-mediated allograft injury and reducing inflammation in the allograft, without affecting the immune system in such a way to risk serious infections. Plasmapheresis and intravenous immunoglobulin are the main treatments

with other therapies such as Rituximab also used. AMR may stabilise, progress or indeed reverse but mortality is usually high. AMR is a major risk factor for the development of chronic rejection and CLAD [134, 135].

Chronic Lung Allograft Dysfunction

Beyond one year after LTx, the greatest threat to survival is the onset and progression of CLAD. This includes a range of pathologies leading to a late and persistent decline in lung function and has been defined as a drop of FEV1 and/or FVC to ≤80% of baseline for ≥3 weeks. Patients present with decline in lung function manifest by symptoms of dyspnea, cough, infections and worsening FEV1 on spirometry [136].

CLAD is predominantly a consequence of chronic rejection, and there are three phenotypes each with typical histopathological findings: obstructive (bronchiolitis obliterans syndrome, BOS), restrictive (restrictive allograft syndrome, RAS) and neutrophilic reversible allograft dysfunction (NRAD), also known as azithromycin-responsive allograft dysfunction (ARAD): a subset of patients whose FEV1 improve after treatment with azithromycin, which has immunomodulatory as well as antibiotic properties [134, 135].

BOS is the clinical correlate of the pathological process of obliterative bronchiolitis or chronic rejection and is defined as a persistent and progressive decline in FEV1 after LTx which is mostly irreversible. Once BOS is diagnosed, the median survival is restricted to approximately 2.5 years.

Patients with RAS demonstrate a restrictive pattern on spirometry and chronic decline in FEV1 of at least 20% and a drop in total lung capacity (TLC) of at least 10%. RAS account for around 30% of all patients with CLAD and have an even lower survival than those with BOS [135].

Risk factors for the development of CLAD include PGD, rejection (acute cellular, antibody-mediated and lymphocytic bronchiolitis), infections (viral/bacterial/fungal), GORD, autoimmunity and persistent bronchoalveolar lavage (BAL) neutrophilia. Chronic rejection is usually diagnosed by spirometry and imaging, although BAL may be used to differentiate between subtypes such as BOS and NRAD [124].

Efforts should be made to identify the reasons behind decline in lung function and causes of CLAD. Treatment options are limited and evidence favouring specific treatment is lacking. Prevention of CLAD is best accomplished by avoiding precipitants i.e. rejection, infection and GORD with adequate immunosuppression and infection prophylaxis. Established CLAD does not respond well to medical therapies and management options include modifying the immunosuppressive treatments, addition of methotrexate, cyclophosphamide, montelukast, total lymphoid irradiation, extracorporeal photopheresis (ECP) and re-transplant in highly-select patients [137].

Malignancy

LTx recipients have a 60-fold increase risk of malignancy compared with the general population with a five year incidence of almost 20%. The two commonest malignancies are skin cancer and PTLD. Post-transplant malignancy may arise from either de novo carcinogenesis, direct transmission of tumors that pre-existed in the donor or recurrence of a recipient's pre-transplant malignancy. Long-term use of immunosuppressants predisposes patients to malignancies due to the direct oncogenic effects [126, 138].

Other Complications, Immunosuppressant Drugs and Pharmacotherapy

In addition to infections, malignancies and side effects affecting cardiovascular, renal, neurologic and gastrointestinal systems as mentioned above; haematological complications may occur primarily bone marrow suppression from azathioprine, mycophenolate mofetil, valganciclovir

or trimethoprim/sulfamethoxazole. Metabolic complications include osteoporosis and osteopaenia. LTx recipients are likely to require a multitude of drugs, and there should be vigilance for drug-interactions.

Self-study

1. Primary graft dysfunction is:
   a. An early complication, defined by diffuse alveolar infiltrates and oxygen impairment
   b. A late complication associated with viral infections
   c. A type of acute rejection
   d. A complication that occurs only in patients with Cystic Fibrosis
2. In severe primary graft dysfunction (PGD3):
   a. There is no indication to retransplantation
   b. ECMO support might be useful to support refractory hypoxemia and give time to the graft to recover
   c. ECMO is contraindicated
   d. VA ECMO is the only therapeutic option
3. Airway complications:
   a. Occurs always late after transplantation
   b. Are rare after lung transplantation
   c. Are caused exclusively by acute rejection
   d. Are common and the stenosis is the most frequent (15%): main causes are ischemia, infection and rejection
4. In the early phase after lung transplantation:
   a. There is high probability of bacterial and fungal infections
   b. There is high probability of viral and opportunistic infections
   c. Infections depends only on donor potential infections
   d. Infections occur only in colonized recipients
5. Chronic lung allograft dysfunction
   a. Is an early complication after lung transplantation
   b. Is different from bronchiolitis obliterans syndrome
   c. Represents a range of pathologies leading to a late and persistent decline in lung function
   d. Should be treated with different interventions, focused on depleting circulating antibodies, suppressing B-cells and mitigating further antibody mediated allograft and reducing inflammation, without affecting the immune system in such a way to risk serious infections

Answers

1. Primary graft dysfunction is:
   a. An early complication, defined by diffuse alveolar infiltrates and oxygen impairment CORRECT
   b. A late complication associated with viral infections
   c. A type of acute rejection
   d. A complication only in patients with Cystic Fibrosis
2. In severe primary graft dysfunction (PGD3):
   a. There is no indication to retransplantation
   b. ECMO support might be useful to support refractory hypoxemia and give time to the graft to recover CORRECT
   c. ECMO is contraindicated
   d. VA ECMO is the only therapeutic option
3. Airway complications:
   a. Occurs always late after transplantation
   b. Are rare after lung transplantation
   c. Are caused exclusively by acute rejection
   d. Are common and the stenosis is the most frequent (15%): main causes are ischemia, infection and rejection CORRECT
4. In the early phase after lung transplantation:
   a. There is high probability of bacterial and fungal infections CORRECT
   b. There is high probability of viral and opportunistic infections
   c. Infections depends only on donor potential infections
   d. Infections occur only in colonized recipients
5. Chronic lung allograft dysfunction
   a. Is an early complication after lung's transplant
   b. Is different from bronchiolitis obliterans syndrome

c. Represents a range of pathologies leading to a late and persistent decline in lung function CORRECT
d. Should be treated with different interventions, focused on depleting circulating antibodies, suppressing B-cells and mitigating further antibody mediated allograft and reducing inflammation, without affecting the immune system in such a way to risk serious infections.

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Size Matching in Lung Transplantation

Alexandru Mihai Cornea, Claudiu E. Nistor, and Alina Ligia Cornea

Abbreviations

SM	Size Matching
TLC	Total Lung Capacity
FEV1	Forced Expiratory Volume per second
FVC	Forced Vital Capacity
pTLC	Predicted Total Lung Capacity
D/R TLC	Donor-to-Recipient TLC
TLV	Total Lung Volume
PFT	Pulmonary Functional Tests
3D-CT	Three-Dimensional Computed Tomography
BOS	Bronchiolitis obliterans syndrome
PGD	Primary Graft Dysfunction
AC	Airway Complications
LT	Lung Transplantation
SLT	Single Lung Transplantation
BLT	Bilateral Lung Transplantation
RLD	Restrictive Lung Disease
RAS	Restrictive Allograft Syndrome
LDLLT	Living Donor Lobar Lung Transplantation
ddLLT	Deceased Donor Lobar Lung Transplantation
CLT	Cadaveric Lung Transplantation
IPF	Idiopathic Pulmonary Fibrosis
COPD	Chronic Obstructive Pulmonary Disease
LLT	Lobar Lung Transplantation

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Key Points

1. Predicted total lung capacity is routinely used to size-match donor and recipient for lung transplantation.
2. Lung volumes can also be estimated from morphometric chest measurements or three-dimensional computed tomography.
3. Oversizing the donor allograft in lung transplantation is usually better tolerated than under-sizing and has a protective effect against PGD or BOS.
4. Inappropriate size-matching increases the risk of post-transplant complications including primary graft dysfunction, airways and vascular complications.

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Introduction

Lung transplantation (LT) is now part of the standard treatment for end-stage pulmonary diseases. Size-matching of donor and recipient is a key factor in selecting the right organ for the right patient. In recent years, pulmonary function tests and three-dimensional computed tomography volumetry (3D-CT) have been used to refine lung volume estimation.

Markers Used for Size Matching

1. **Height** is the most commonly used surrogate for lung size matching since donors and recipients of the same gender with similar heights would have comparable lungs volumes [1].

However, if lung allocation was solely based on height, there is potential for errors because other criteria including gender, race and weight can also influence lung volume. Male lungs are 20% larger than females. Therefore, female donor lungs should generally be implanted in smaller male recipient whereas male lungs should be implanted in a taller female recipient.

2. **Predicted Total lung capacity (pTLC)**

Total lung capacity is the volume of the air within the lungs at the end of a maximum inspiratory effort. Usually TLC ranges between 4 and 6 litres but it depends on height, gender and age.

Predicted total lung capacity is calculated by a regression formula which correlates height and sex. According to European Respiratory Society [2] pTLC for males = 7.99H − 7.08 and for females pTLC = 6.60H − 5.79 where H is height in meter.

These equations are used for Caucasians between 18–70 years old and 1.55–1.95 m (males) and 1.45–1.80 m (females).

Oversized donor lungs may increase the risk of atelectasis, infections and impaired ventilation. Undersized donor lungs can result in a high negative intrathoracic pressure after transplantation with risk of pneumothorax, empyema, BOS and obstructive lung disease. The degree of size mismatch can be evaluated by the D/R pTLC ratio = donor pTLC/recipient pTLC. Patients can be grouped as pTLC-ratio > 1.0 (oversized) or pTLC-ratio <= 1.0 (undersized).

Eberline [3] had shown that an oversized allograft (pTLC-ratio > 1.0) has higher expiratory flow capacity and less frequent incidence of BOS and primary graft dysfunction.

In obstructive lung disease the aim is to have 10–20% volume larger lungs than predicted values. Hyperinflation caused by emphysema results in a larger recipient chest cavity and using pTLC may undersize the lung. In restrictive lung disease such as interstitial lung disease, pTLC will oversize the lung allograft because the pleural space and chest cavity are contracted.

3. **Actual TLC** (aTLC) as total lung capacity measured by computed tomography is more accurate than calculated pTLC because actual lung volumes correlates better with the underlying lung disease.

The differences between pTLC and actual TLC were statistically greater in restrictive group than obstructive one and the ratio of aTLC to pTLC was 77% for obstructive and 57% in restrictive group [4]. Despite these benefits CT evaluation of aTLC in patients with end-stage lung disease and respiratory impairment is difficult and can give rise to errors.

4. **Pulmonary function tests** make use of spirometry to provide forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC), measured as FEV1/FVC ratio.

5. **Three-dimensional computed tomography**

Is used for volumetric lung assessment as “anatomical size matching” on both recipient and donor (in living donor lung transplantation). The patients are instructed to hold their breath at the end of a deep inspiration. The images are processed, and manual and automatic segmentation

are performed. Thereafter the lung volumes are correlated with PFT results. 3D-CT volumetry can measure the right and left lung volumes (TLV) individually which is particularly useful when there is gross asymmetry between the two sides.

6. **Forced Vital Capacity**

Forced Vital Capacity is the volume of air that can be forcefully exhaled in a single breath from maximal inspiration to maximal expiration. This is predominantly used in evaluate for living donor lung transplantation (LDLLT) for "functional" size-matching.

Date [5] described a segment-based formula for estimating graft FVC, based on donor FVC. The right lower lobe is considered to have 5 segments and left lower lobe has 4 giving; a total of 19 segments for the two lungs. The estimated graft FVC = (Measured FVC of the right lower lobe donorx5/19) + (Measured FVC of the left lower lobe donorx4/19).

If the estimated graft FVC were larger than 45% of predicted recipient FVC, the donor are considered potential suitable for LDLLT.

7. **3D-CT Angiography**

Was developed in early 1990 for preoperative evaluation of pulmonary artery, vein and bronchi variations for LDLLT [6].

Preoperative assessment of the donor and recipient vessels and bronchial anatomy can offer anatomical information to assist surgical planning of donor lobectomy and recipient lobar transplantation.

8. **Biphasic computed tomographic volumetry**

Inspiratory to expiratory computed tomography volumetry (I/E CT volumetry) has been proposed as a way to detect unilateral CLAD following LDLLT [7]. I/E CT images are obtained after a maximum inspiratory effort and expiratory effort with a multidetector scanner. The 3D lung models are reconstructed and lung volume is calculated by subtracting expiratory lung volume from inspiratory lung volume. In unilateral CLAD lung volume of the rejection side is reduced by 20% or more.

In BOS both inspiratory and expiratory volumes are increased whereas in RAS, both volumes are decreased.

Complications of Inappropriate Size Matching

Primary graft dysfunction (PGD) is a complication of LTx which develops within the first 72 hours. It presents as acute respiratory failure with hypoxia, pulmonary infiltrates and alveolar damage [1]. PGD is a risk factor for bronchiolitis obliterans syndrome (BOS), CLAD and death. The ISHLT diagnostic criteria are PaO_2/FIO_2 ratio and radiographic infiltrates and signs of pulmonary oedema (for more information, please refer to chapter "Anterior Surgical Approach to the Abdominal Aorta").

Hyperinflation of undersized donor lung grafts may result from higher tidal volumes set in according with recipient rather than donor weight, which increase the risk of ventilator-related lung injury and early graft failure. This could be avoided by using a protective ventilation regime and tidal volume calculated from the donor weight instead.

Bronchiolitis obliterans syndrome (BOS) is a complication which can be triggered by undersized grafts, the related mechanism is small airways obstruction due to immune or nonimmune damages on epithelium and alveoli by repeated trauma induced by hyperventilation and inflammation. Clinically, it manifests by a permanent decline in FEV1 of 20% of more. Airway obstruction lead to fibrosis and graft failure.

In oversized grafts, because of chest wall strapping mechanism, the patient is breathing with lower lung volumes and there is less epithelial injury. Consequently, the risk of PGD is lower.

Donor-recipient size mismatch-related complications [8] are not uncommon because of the altered chest geometry in obstructive (chest enlargement) or restrictive diseases (chest

contraction). Bilateral lung transplantation of oversized lungs can compromise the haemodynamic because of the increased intrathoracic pressure of the ventilated lungs. If the donor lungs are too large for the recipient chest cavity, downsizing procedures on the donor lung may be required.

Non-anatomical downsizing procedures are simple to perform but have the risk of air-leak from the stapling lines.

Anatomical downsizing such as segmentectomies, lingula excision, or lobectomies are safe and can be performed if necessary. In some circumstances of an extreme large donor lung, leaving the chest open is a practical option.

In lobar LTx, if the donor lobe is smaller than the chest cavity, a native upper lobe sparing procedure [9] or right to left lobar LTx are potential options.

Size Matching in Single Lung Transplantation

Barnard et al. [10] reviewed the evidence base of size matching and presented their recommendations (Table 1).

For patients with idiopathic pulmonary fibrosis (IPF), using recipient actual TLC for sizing is inappropriate due to their contracted chest cavity. It would be more appropriate to use pTLC in combination with other radiologic and physiologic criteria (Level B). In IPF patient undergoing single lung transplant, it is probably feasible to match the donor pTLC to within 15–20% above or below the recipient pTLC. (Level C recommendation). In the IPF recipient, there is differential tolerance to size discrepancies between the two chest cavities: in the left chest, the donor lung expands to its native size; on the right, a donor lung can only expand to the recipient's thoracic cavity volume. It has been suggested that in IPF patients with reduced aTLC undergoing SLT, donor lungs with pTLC more than double that of the recipient aTLC can be tolerated without downsizing because of the chest wall adaptability by mediastinal shift.

For a recipient with emphysema, aTLC is usually greater than the pTLC. Therefore, using recipient pTLC to determine suitable donor lungs would likely undersize an allograft. The recipient chest wall factors determine post-operative pulmonary function in patients undergoing SLT for COPD. Hyperinflation does not affect donor allograft function. One study has shown a correlation between infra-mammary circumference ratio and post-operative FEV1 at 3 months with optimal outcome when the donor:recipient ratio is 0.89.

Loizzi [15] has studied ratio of donor pTLC to recipient pTLC and aTLC as an objective criterion for lobar versus entire lung transplantation. The conclusion was that the donor to recipient pTLC ratio is more useful than the donor pTLC versus recipient aTLC ratio in discriminating between lobar or entire lung transplantation.

Size Matching in Bilateral Lung Transplantation

An analysis data of the thoracic organ transplant registry showed that higher pTLC-ratios (>1) are correlated with improved survival with a reduced incidence of PGD and reduced length of hospital stay [12]. In undersized allografts, higher tidal volumes may result in higher pulmonary vascular resistance and early graft failure. In contrast, oversized grafts tend to have lower tidal volumes of ventilation and lower pulmonary vascular resistance because there is a correlation between inflation status and PVR.

Thus, oversizing the allografts in BLT are beneficial in terms of reducing posttransplant morbidity and mortality and pTLC ratio remains a useful estimate in BLT.

Transplant Size Matching in Restrictive Lung Disease

For patients with restrictive lung diseases (RLD), using recipient aTLC to determine graft requirement could undersize the graft. Recipient

Table 1 Recommendations for size matching in lung transplantation [10]

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1. Criteria for the acceptable size range of the donor lung pTLC should be decided on at the time of the multidisciplinary team listing meeting. At this time, all available imaging and spirometry for the recipient should be reviewed and used to inform the decision-making process about the acceptable pTLC range of the potential donor (Level C)
2. Patients with emphysema should be matched with donor lungs between 67% and 100% of the recipient's aTLC (Level B) [11] (a) This is demonstrated by the superior post-operative FEV_1, freedom from BOS and survival of patients who receive larger lungs [3, 12, 13] (Level B) (b) The donor lungs should not exceed the aTLC of the recipient, as this would impair chest wall mechanics [11] (Level B) (c) This aim may be limited by the supply of larger sized donors (Level C)
3. There is no clear consensus of evidence for recommended size-matching criteria for patients with emphysema who are being considered for SLT. One study has shown a correlation between infra-mammary circumference ratio and post-operative FEV1 at 3 months with optimal outcome when the donor:recipient ratio is 0.89 [14] (Level C)
4. In patients with pulmonary hypertension or cystic fibrosis, where there is not a large deviation between aTLC and pTLC, there is evidence to support matching the donor pTLC to the recipient pTLC with an upper limit cut-off of up to 120% [15, 16] (Level B)
5. In patients with pulmonary fibrosis, the limitations of using recipient aTLC as a guide to size matching should be recognized [15] and acceptable donor pTLC range should be determined by a combination of radiologic and physiologic assessment (Level B)
6. In pulmonary fibrosis where donor pTLC is considered for SLT it is probably feasible to match donor pTLC to the recipient pTLC within a 15–20% range above or below this figure [17, 18] (Level C)
7. There is no evidence to recommend ideal size matching in BLT for pulmonary fibrosis; however, we suggest that it is safer to accept a donor pTLC in a range 15–20% above or below an ideal target of halfway between the recipient pTLC and aTLC (Level C)
8. Future studies should present data in a format that categorizes results according to native lung pathology and highlights the analyses of patients who were size matched outside of the current recommended range (Level C)

pTLC ratio is a better measure to determine appropriate donor lung sizing.

Ganapathy shows that SLT for RLD with considerable undersizing (D:R pTLC ratio < 0.8) had a significantly increased risk of mortality as well as incidence of airway dehiscence whereas a D:R pTLC ratio close to 0.9 or higher is associated with better survival [19]. Conversely, a D:R pTLC ratio between 1.1 and 1.2 in BLT is associated with increased mortality because a small cavity receives two oversized lungs could diminish mechanical ventilation and could result in tamponade. Overall, survival after BLT is superior to SLT for RLD (see chapter "Approaches and Surgical Techniques in Lung Transplantation" for more details).

Deceased-donor-Lobar lung transplantation (ddLLT) is a surgical option for recipients with small chest cavities who have had a long waiting time list [20]. Eberline proposed a number of formulae for size matching donor and recipient pTLC and donor pTLC after lobar resection (pTLC donor lobar).

One-year survival after ddLLT ranged between 50 and 100% but was less than conventional LTx. The main parameter for sizing ddLLT lungs was the pTLC lobar ratio the downsizing was 0.76 ± 0.2 in a review study. It was declining risk of death with higher pTLC ratio from 0.5 to about 1.3, where an inflection occurred with rising risk at pTLC > 1.3 [10].

Isolated upper or lower lobar transplants have the advantage of avoiding bronchial stumps as in bi-lobar transplantation, despite the size-mismatch between the recipient main bronchus and donor lobar bronchus. The main airway complication in ddLLT is anastomotic stenosis.

For IPF patients, the aim is to have a donor TLC around 150% of the recipient pTLC. Bilateral ddLLT using lower lobes is preferred because the lower lobes fit anatomically better in the chest cavity and the risk of residual air space is less than for upper lobe transplants. Because of the relocation of the lower lobe after inflation, it is crucial to adjust the length of the pulmonary artery to avoid kinking.

Size Matching in Living Lobar Lung Transplantation (LDLLT)

Because we use two lobes from two living donors size matching with the recipient is particularly important. Sometimes the lobe grafts are too small and there is a risk of pulmonary oedema, high pulmonary resistance, and finally failure of the graft. In the other situation that the lobar grafts are too big because of adult donor and a small recipient than hemodynamic instability, atelectasis, and infection develop. For size matching in LDLLT Date [5] uses FVC as "functional" SM for undersized living donor allografts assessment. The graft FVC formula was presented earlier in the chapter. Lower acceptable threshold of total FVC of the two donor grafts is 45% of the predicted recipient FVC.

"Anatomical" size matching follows a volumetric size matching for oversized living donor lobar allografts. 3D high speed multi-slice CT is performed, with image reconstruction and automatic lung volume calculation. There upper threshold of the volume is around 200%.

When the right and left lower lobes are implanted to normal size adults the grafts are usually undersized. The surgical way out is to spare the native upper lobe to add more volume to the transplanted lobes or to do a right-to-left inverted lobar transplantation.

The indication for *native upper-lobe sparing LDLLT* [5] is when two lobes are too small for an adult and the D:R FVC graft ratio is less than 60%.

The surgical technique involves anastomosis of the donor bronchus to the second carina, donor pulmonary vein to the recipient inferior pulmonary vein and donor pulmonary artery to the recipient interlobar artery in the fissure [9].

Right-to-left inverted lobar transplant is used in undersized grafts by implanting the right lower lobe into left chest cavity thus adds 5 lung segments instead of 4 as left lower lobe has [5].

Multiple-Choice Questions About Size Matching in Lung Transplantation

Self-study

Question 1:
Which of the following parameters are estimates for lung transplantation size matching?

A. Forced Vital Capacity
B. Height
C. Predicted total lung capacity
D. Three-Dimensional computed tomography
E. Weight

Correct answers: A, B, C, D

Question 2:
Which estimate is used as "functional" size matching in LDLLT?

A. 3D-CT
B. Actual TLC
C. FVC
D. Predicted TLC
E. Weight

Correct answer: C

Question 3:
Which estimate is used for "anatomical" size matching in LDLLT?

A. 3D-CT
B. FEV1
C. FVC
D. Height
E. Predicted TLC

Correct answer: A

Question 4:
Which estimate is better correlated with lung size matching in restrictive lung diseases?
A. 3D-CT
B. Actual TLC
C. Predicted TLC
D. Height
E. Weight

Correct answer: C

Question 5:
Which complications after lung transplant are donor-recipient size mismatch related?
A. Anastomotic leakage
B. Bronchial dehiscence Bronchiolitis obliterans syndrome
C. Bronchial fistula
D. Bronchiolitis obliterans syndrome
E. Primary graft dysfunction

Correct answer: A, B, C, D, E

Question 6:
Which are the clinical features of posttransplant pulmonary vein stenosis?
A. Chest pain
B. Cough
C. Pulmonary oedema
D. Shortness of breath
E. White-out on chest X-ray

Correct answer: A, B, C, D, E

Question 7
Which of the donor-recipient size-related complications are characteristic for oversized lungs?
A. Air-fluid collection
B. Atelectasis
C. Haemodynamic collapse
D. High pulmonary vascular resistance
E. Infection

Correct answer: B, C, E

Question 8:
Which of the following surgical procedures is used in oversized grafts?
A. Middle lobectomy
B. Right-to-left LDLLT
C. Segmentectomy
D. Single lung transplant
E. Upper lober sparing LDLLT

Correct answer: A, C, D

Question 9
The segment-based estimation formula was described for donor-recipient size matching in LDLLT as:
A. 3D-CT volumetry formula
B. FVC estimation formula
C. Height
D. Predicted TLC regression formula
E. TLV formula

Correct answer: A, B

Question 10
In donor-recipient size-matching for lung transplantation which of the following statement(s) is/are true?
A. 3D-CT volumetric data is used is SM because it offers true volume data
B. D/R pTLC ratio is a good estimate for single lung transplant in pulmonary fibrosis recipients
C. FVC is a surrogate for anatomical SM in LDLLT
D. TLV volumes are better correlated with recipient pTLC than aTLC
E. None of the above

Correct answers: A, B, C

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Lobar Transplantation

Mustafa Vayvada and Ahmet Erdal Taşçı

Key Points

- Donor organ shortage remains a major problem in lung transplantation and many patients die on the waiting list.
- The estimated total lung capacity of the donor is recommended to be 75–125% of the recipient's predicted total lung capacity.
- An acceptable range of donor total lung capacity should be determined by radiological and physiological assessments.
- Size mismatch between donor lung and recipient thoracic cavity volume can have an important impact on outcomes.
- Problems of oversized graft include suboptimal chest wall mechanics, a tamponade effect and aatelectasis.
- Lobar lung transplantation is a technique applied in pediatric and adult patients in need of smaller-sized donor lungs.

Cadaveric Lobar Lung Transplantation

Since the first successful single lung transplantation performed by Cooper et al. in 1983, lung transplantation (LTx) has gained an important place in the treatment of late-stage lung diseases. With the increase in the number of LTx over the years, survival rates have gradually improved. However, since the number of cadaver donor lungs has not increased at a sufficient level in parallel with the increase in the number of potential transplant candidates, there are problems in finding compatible donors. End-stage lung disease patients, and especially patients with small thoracic cavity such as in pulmonary fibrosis and cystic fibrosis, have to wait longer times for donor lungs of compatible sizes.

The use of cadaveric lobar lung transplantation is gradually increasing in an attempt to expand the pool of potential donors for patients who have worsened during the long waiting periods or who are in a critical condition. However, although lobectomy is a well-known standard and simple method, lobar lung transplantation is not routinely performed. In 1994, Bisson et al. reported the first cadaveric bilateral lobar lung transplantation in two recipients with cystic fibrosis. In these cases, they transplanted the left lower lobe and the right lower and middle lobes [1]. Subsequently, together with other

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centers, they reported their experiences on donor lung size reduction [2].

Anatomic Size Matching Between Donor and Recipient

Size compatibility is an important issue for lung transplantation that has an important impact on the clinical results. Size mismatch has been shown to be associated with longer lengths of stay on the intensive care unit, permanent atelectasis, expansion defects, hyperinflation, decreased exercise capacity and obliterative bronchiolitis syndrome [3].

The best size matching method is still a matter of debate. Commonly used strategies include chest X-ray comparison between donor and recipient; calculation of the ratio of patient heights; calculation of the predicted total lung capacity (pTLC) ratio; and estimation based on visual examination in the operating room [4] (Picture 1). Three-dimensional computed tomography (3D-CT) volumetry is a new and reliable method for the evaluation of lung volume. It has been shown that the total lung capacity (TLC) calculated using 3D-CT volumetry is well correlated with the lung volume measured by the use of spirometry, and that it can be used in the evaluation of respiratory function [5, 6].

It has been shown that if the donor pTLC is between 75 and 125% of the recipient pTLC, there will be no clinical or functional negative effects observed following heart-lung transplantation and bilateral lung transplantation [4–7]. Prediction of the donor TLC is important for optimum size matching and different methods have been recommended to this end.

For cadaveric LTx, it is possible to predict the donor TLC using a formula based on donor height and gender [8].

Donor pTLC (liters);

$$\text{For male donors, pTLC} = 7.99 \times \text{height in meters} - 7.08$$

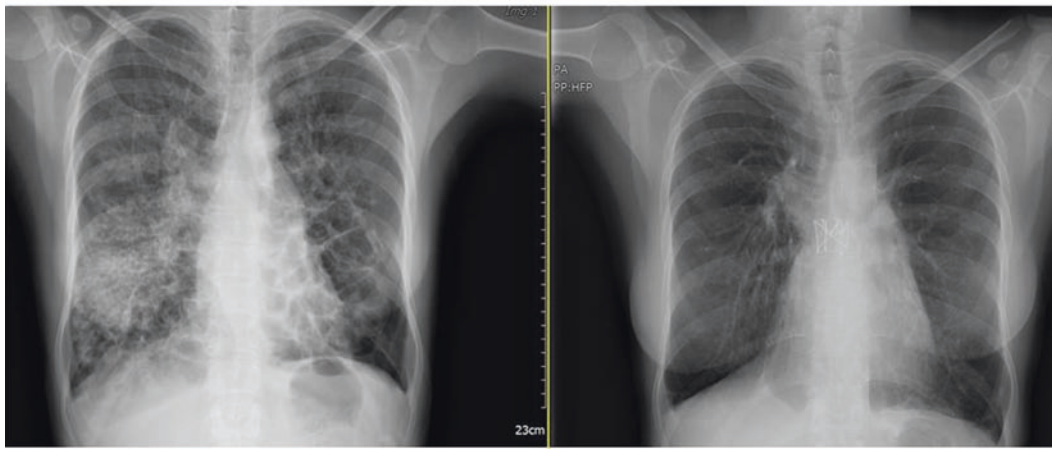
$$\text{For female donors, pTLC} = 6.6 \times \text{height in meters} - 5.79.$$

In order to calculate the total lung capacity of a lung after a certain number of segments has been resected (sr-TLC):

$$\text{sr-TLC} = \text{pTLC} \times (1 - \text{S} \times 0.0526),$$

$$\text{S} = \text{number of resected segments}$$

Published standard reference equations based on height and age can also be used for size matching of the lung between the donor and the recipient [9, 10].



Picture 1 **a** Preoperative chest X-ray. **b** 1 year postoperative X-ray

For adult male donors: TLC = 0.094 × height (cm) − 0.015 × age (years) − 9.167

For adult female donors: TLC = 0.079 × height (cm) − 0.008 × age (years) − 7.49

For donors of age ≤ 16 years old: TLC = 0.001002 × (height^2) − 0.22713 × height + 15.1397

However, volume predictions based only on age or height can be misleading. The thoracic volume of children is different compared to adults, and the thoracic cavity tends to be larger in male patients. Disease diagnosis of the recipient can also influence the thoracic volume. For instance, the thorax cavity is larger in patients with emphysema, while being smaller in patients with fibrotic conditions. In patients who develop pulmonary hypertension, lung volume can decrease due to cardiomegaly [4]. It is unclear whether the donor pTLC has any predictive value on the postoperative recipient lung function, especially in cases where the donor lung size has been reduced.

Surgical Technique

Due to the limited donor pool, volume reducing operations can be performed on larger donor lungs instead of turning down these organs. Of the available techniques, peripheral wedge resection is the most commonly performed, targeting the middle lobe or lingual segment. However, prolonged air leak is a significant risk with this approach. Loizzi et al. reviewed recipient who had standard lung and lobar transplantation, and concluded that the donor/recipient pTLC ratio should have an upper limit of 1.15–1.20, and that lobar transplantation should be performed in case it is >1.20 [11].

Anatomic resections such as segmentectomy, lobectomy and bilobectomy can be performed. Lobar and split-lung transplantation are the other options.

When an unexpected size mismatch is encountered during the transplant, there can be a dilemma of which technique to apply. Middle lobectomy decreases the donor lung capacity in the anteroposterior aspect, and is most appropriate for thin recipients that have a smaller anteroposterior diameter. Lower lobectomy is more appropriate for recipients with a high diaphragm, e.g. patients with pulmonary fibrosis. Upper lobectomy decreases the donor lung volume in the vertical aspect; however, with the residual lung parenchyma mainly below the hilum, this has the potential for creating an apical gap. Tackling a basal gap is generally easier compared to an apical gap, since the diaphragm can simply move upwards in the latter situation. Which lobe is to be excised should also take into account of the condition of the donor lung, such as severe contusion of the lower lobe, bullous disease or scarring of the upper lobe.

Size reduction lobectomy can be performed back-table or after implantation. Back-table lobectomy saves time, since it can be performed by another surgeon simultaneously with the preparation of the recipient. Furthermore, it avoids the situation of a large donor lung obscuring the view of the hilum within a small chest cavity. Finally, back table dissection allows for direct anastomosis between the donor lobar bronchus and recipient main bronchus. Therefore, the bronchial stump that is unavoidable in post-transplantation lobectomy does not occur in back-table lobectomy. However, with the lack of blood circulation in the pulmonary vessels, back-table lobectomy can sometimes be difficult. On the other hand, performing post-transplantation lobectomy can also be challenging due to having an oversized lung within a small chest cavity. Another disadvantage of post-implant lobectomy is that it can cause further injury to the transplanted lung through surgical manipulation of the recently reperfused lung.

Upper lobectomy of the donor lung is performed in order to transplant the middle and lower lobes on the right side. In this technique, the oblique fissure is dissected and the interlobar pulmonary artery is prepared. The upper lobe vein is then divided in such a way that does not distort the atrial cuff, which includes both the

superior and inferior veins. The upper part of the oblique fissure between the upper and lower lobes and the horizontal fissure between the upper and middle lobes can be separated with a stapler. Upper lobe branches of the pulmonary artery are dissected free, ligated and divided. The donor intermediary bronchus is transected only one ring above the apical segmental bronchus of the lower lobe, and attention is paid to preserving the peribronchial connective tissue. The main advantage of transplanting the lower and middle lobes is a reasonable size match between the diameter of the donor intermediary bronchus and the recipient main bronchus. The biggest disadvantage is the risk of distorting the inferior pulmonary vein. A large pericardial cuff or donor aorta graft can be used to widen the donor left atrial cuff to protect the venous flow from the middle lobe (Picture 2). The donor pulmonary artery should be kept long enough to allow anastomosis without any tension.

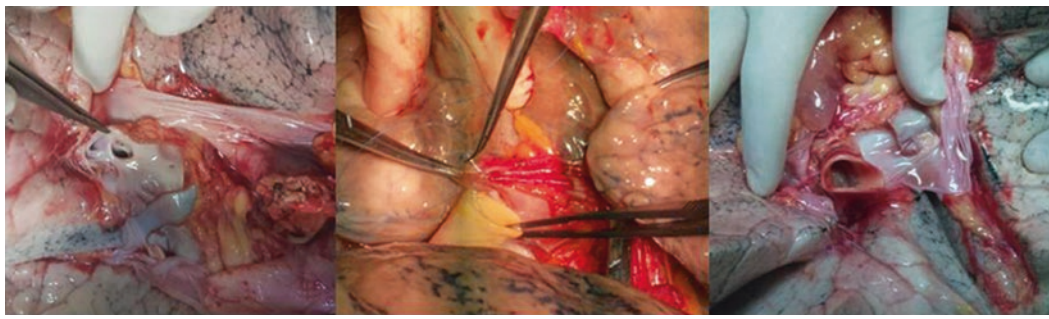
To implant the right upper lobe only, the oblique fissure is separated, and the interlobar pulmonary artery and middle lobe artery are dissected and divided while protecting the posterior ascending artery. The inferior and middle veins are dissected, ligated and divided taking care not to distort the left atrial cuff. The upper lobe bronchus is divided at its origin on the donor main bronchus.

To implant the upper and lower lobes only, the middle lobe is resected. The middle lobe vein and artery are dissected, ligated and divided. If the transverse fissure is incomplete, the upper and middle lobes can be separated using a stapler. The middle lobe bronchus is divided with the stapler; the main donor bronchus is divided one ring above the secondary carina.

To implant just one lobe from the left lung and excise the other lobe, the oblique fissure is opened and parenchymal attachments between the upper and lower lobes are divided with a stapler. The interlobar pulmonary artery is exposed. To implant the left lower lobe alone, the left upper lobe is excised by ligating and dividing arterial branches to the upper and lingual lobes. The superior pulmonary vein is disconnected from the left atrial cuff without distorting the latter. The left lower lobe bronchus is divided one ring proximal to the apical segment bronchus of the lower lobe.

To implant the left upper lobe only, the left lower lobe is excised by ligating and dividing arterial branches to the lower lobe. The inferior pulmonary vein is disconnected from the left atrial cuff without distorting the latter. The upper lobe bronchus is divided at the level in which it connects with the main bronchus.

Perioperative management and postoperative care in lobar LTx differ from that of standard LTx. Patients who are candidates for lobar LTx tend to be higher risk recipients. Following implantation of the first lobe and during the pneumectomy dissection of the second native lung, almost all the cardiac output goes to the implanted lobe. The limited vascular bed of the recently reperfused lobe together with the sudden surge in blood flow frequently result in increased pulmonary pressure, extravascular



Picture 2 Donor lung atrium injury and reconstruction with aortic graft

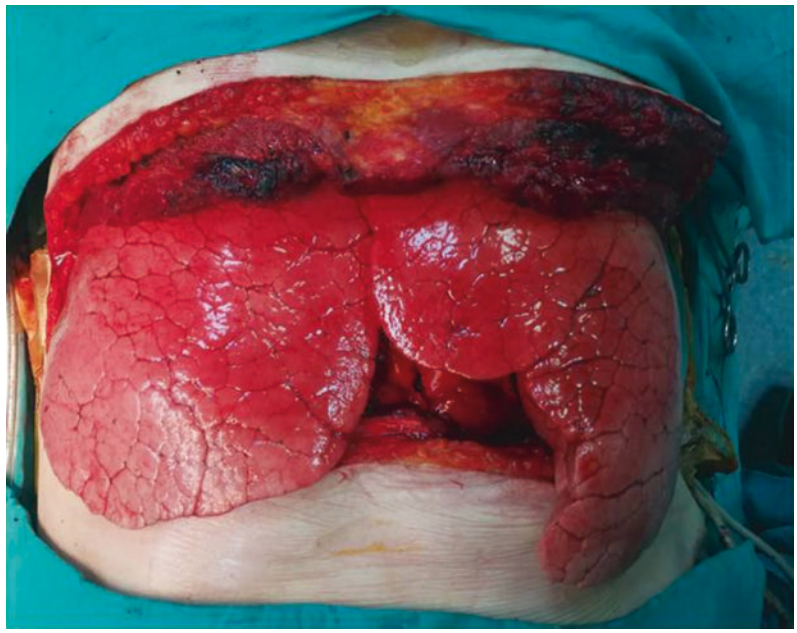
fluid leakage and lung edema. Cardiopulmonary bypass (CPB) limits the pulmonary blood flow during this time and could prevent overloading of the pulmonary vascular bed [12]. In recent times, the use of peripheral or central venoarterial ECMO, which requires less heparin, has been favored over the use of CPB [13, 14].

Split implantation of the left donor lung has also been described. The donor left lower lobe was implanted in the recipient's left thorax cavity and the left upper lobe was implanted into the right. The right donor lung can then be transplanted into another patient thereby making the best use of the available donor lungs [15, 16].

Oversized and Undersized Graft

In LTx, inappropriate size match could negatively impact post-transplant outcomes and survival. It has been shown that an excessively large graft could result in atelectasis, distorted diaphragm movement, high pulmonary vascular resistance and impaired gas exchange through shunting. Greater attention should be paid to size matching, especially for emphysematous patients in which the chest wall and diaphragm movement are distorted and hyperventilation is predominant. If there is uncertainty regarding the resection size required, or the recipient becomes unstable on attempts at chest closure, the chest wall can be left open, with only skin closure [17]. The amount of size reduction can be subsequently decided once the lung reperfusion edema has settled and the transplanted lung has adapted to the recipient chest cavity. This will help prevent the post-transplantation respiratory problems associated with the resection of too much lung tissue (Picture 3).

The most common complication observed immediately after LTx is primary graft dysfunction (PGD). This manifests within the first 72 hours after LTx through widespread pulmonary infiltrates and hypoxia. Implanting an undersized donor lung into a large chest cavity and mechanical ventilation with high tidal volume caused by size mismatch early is an important risk factor [18]. Small grafts can also lead to increased risk of postoperative bleeding and higher pulmonary vascular resistance, persistent pleural spaces, pleural effusion and infection.



Picture 3 Delayed chest closure after lung transplantation

It has been demonstrated that oversizing lungs can increase survival in the presence of pulmonary hypertension. Eberlein et al. found that the median survival of LTX recipients with donor/recipient pTLC ratio of 1.24 ± 0.1 is 831 days longer when compared to patients with D:R pTLC ratio of 0.93 ± 0.1 [19].

Conclusion

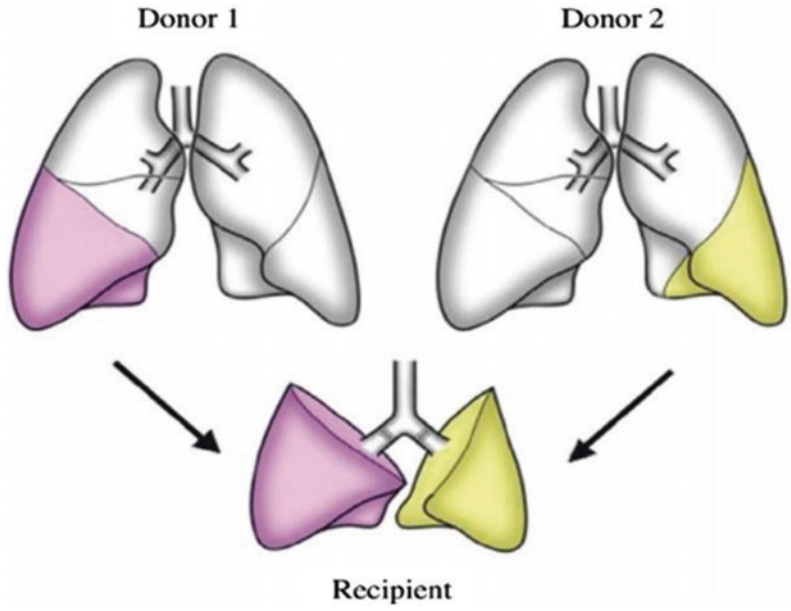
Results reported by various groups show that lobar lung transplantation can be performed with an acceptable level of risk in patients that have an urgent need for small donor organ, so as to decrease the mortalities observed while these patients are waiting.

Living Donor Lobar Lung Transplantation

Key Points

- Lobar lung transplantation from a live donor can be life-saving for recipients with end-stage lung disease who cannot be expected to survive until a cadaveric organ becomes available due to deterioration of lung function and clinical conditions.
- Lobar lung transplantation is an alternative to cadaver lung transplantation.
- The right and left lower lobes from two separate larger donors are implanted in the recipient instead of the whole right and left lung.
- The most important feature that distinguishes donor lobectomy from standard lobectomy is the preservation of adequate arteries, veins and bronchial stumps, which allows the anastomoses to be performed at the implantation stage.
- The ideal timing for offering living donor lobar lung transplantation is controversial.
- Because of the surgical risks that the live donors are exposed to through donating one of their lobes, cadaver lung transplantation is preferred. However, live lobar lung transplantation should continue to be considered in appropriately selected cases.

Lobar lung transplantation from live donor was first described by Starnes et al. [20] for pediatric patients with an urgent indication for LTx.



Picture 4 The right lower lobe from the first donor is on the right side of the recipient, the left lower lobe from the second donor is implanted on the left side [24]

In this procedure, the right lower lobe is taken from one of the two adult live donors whilst the left lower lobe is taken from the other donor, and both are then implant into the recipient (Picture 4). Since this procedure requires two healthy donors to undergo lobectomy and exposing them to major surgical risks, living donor lobar lung transplantation (LDLLT) potentially puts three people at risk while only offering the chance to improve the quality of life for one [22]. This has at times raised ethical concerns. The transition to the lung allocation scoring system in the United States has brought with it a decrease in the waiting list mortality [21]. This has in turn led to a decrease in the use of LDLLT. Although its use is decreasing worldwide, centers in Japan have continued to perform this procedure and further developing it due to the rarity of cadaveric organ donors in that country [23].

Patient Selection

Similar criteria apply for the selection of candidates for cadaver and live donor LTx. The generally-accepted approach is to consider offering LDLLT to patients who are gradually deteriorating on the waiting list and who are not expected to survive the long waiting times, but who are, at the same time, predicted to have the necessary reserve to recover from this major surgery. While in the United States and Europe, LDLLT tends to be performed more on cystic fibrosis patients, in Japan, it is performed for a wide range of diagnoses including pulmonary hypertension, idiopathic pulmonary fibrosis, bronchiolitis obliterans, bronchiectasis and lymphangioleiomyomatosis.

Criteria to be live lobar donor; [24]

Age: Between 20 and 60 years,
Absence of a history of previous surgical interventions on the donor lung side,
Absence of an active or intensive smoking history,
Absence of a history of active lung disease on the donor lung side,
Absence of a defined risk of familial lung disease,
Absence of cachexia (body mass index (BMI) < 18 kg/m^2) or obesity (BMI > 30 kg/m^2),
ABO blood type compatibility with the recipient,
Compatibility of the donor lung lobe size with the recipient's hemithorax,
Having normal pulmonary function and normal values for arterial blood gasses,
Absence of conditions that increase the general anesthesia, surgical or postoperative risks,
Absence of psychological and ethical issues or concerns regarding the donor's motivation,
Absence of pregnancy,
Absence of active malignancy,
Absence of a significant active infection (HIV, hepatitis, acute CMV).

After identifying two potentially compatible donors, it is necessary to define the method for comparing the lower lobes of both donors with the optimal size for the recipient. For preoperative evaluation, the Kyoto group choses donor lungs of compatible volume and normal vascular structure by using high definition computed tomography and three-dimensional CT (3D-CT) [25].

During live donor lobectomy, adequate lengths of artery, vein and bronchial stumps should be left so as to allow anastomoses to be performed during implantation. Following fissure dissection, the lower lobe arteries are isolated, and for the right side, the middle lobe artery is also isolated. The pericardium surrounding the inferior pulmonary vein is opened circumferentially. Prostaglandin E1, 10,000 units of heparin and 500 mg methylprednisolone are administered intravenously, after which the lower lobe artery, the inferior pulmonary vein and lower lobe bronchus are divided. On the patient end, the vascular stumps are closed with a 5-0 Prolene continuous suture, while the bronchial stump is closed with a 3-0 Prolene suture supported with pericardial fat tissue. The donated lobe is taken to the back table and

perfused anterogradely and retrogradely with one liter of cold Perfadex solution. During this process, the lobe is gently ventilated with room air [26, 27].

Until the end of 2017, there have been 388 cadaveric LTx performed in Japan compared to 208 LDLLT. For cadaveric LTx, the 5- and 10-year survival rates were 71.7% and 55.7%, respectively. The long-term results of LDLLT were somewhat superior with 5- and 10-year survival rates of 73.4% and 64.1% respectively [28]. Chronic lung allograft dysfunction, and especially restrictive allograft syndrome, is seen later in LDLLT compared to cadaveric LTx, and it is also observed to have a lower impact on overall survival after LDLLT [29].

Conclusion

Although the lung allocation scoring has decreased waiting times and waiting list mortality rates, LDLLT is still considered to be appropriate for young patients who become critical during the waiting period, and for cases in which an organ donor is urgently needed. Although cadaver LTx is preferred due to donor risks, it has been determined that in centers with a good experience of LDLLT, its long-term results are better than that after cadaveric LTx.

Self-study

1. Which statement is true?
   (a) In split lung transplantation, the left lower lobe of the donor is implanted into the left thoracic cavity and the left upper lobe is implanted in the right thoracic cavity.
   (b) Lobar transplantation is more commonly performed than peripheral wedge resection to reduce the volume of an oversized donor lung.
   (c) The estimated total lung capacity of the donor is recommended to be between 60 and 140% of the recipient's pTLC.
   (d) Undersized graft results in atelectasis, distorted diaphragm movement, high pulmonary vascular resistance and poor gas exchange.
2. Which statement/statements is/are true?
   (a) In living donor lobectomy, adequate arteries, veins and bronchial stumps should be maintained to facilitate the anastomoses at implantation.
   (b) Live donor lobar lung transplantation is not an alternative to cadaver lung transplantation.
   (c) Decrease in the lung transplant waiting list mortality has also led to a decrease in the use of living donor lobar lung transplantation.
   (d) a and c.
   (e) b and c.

Answers

1. Which statement is true?
   (a) CORRECT. In split lung transplantation, the left lower lobe of the donor is implanted into the left thoracic cavity and the left upper lobe is implanted in the right thoracic cavity. The estimated total lung capacity of the donor is recommended to be between 75 and 125% of the recipient's pTLC.
   (b) INCORRECT. Peripheral wedge resection is the most common method for volume reduction. Small grafts cause lung hyperextension, persistent pleural spaces, pleural effusion, infection, hyperinflation, increased risk of postoperative bleeding, risk of acute lung damage due to high tidal volume in mechanical ventilation and higher pulmonary vascular resistance.
   (c) INCORRECT. The estimated total lung capacity of the donor is recommended to be between 60 and 140% of the recipient's pTLC.
   (d) INCORRECT. Undersized graft results in hyperinflation, increased risk of primary graft dysfunction and postoperative bleeding, higher pulmonary vascular resistance, persistent pleural spaces, pleural effusion and infection.

2. Which statement/statements is/are true?
   (a) CORRECT
   (b) INCORRECT. Live donor lobar lung transplantation is an alternative to cadaver lung transplantation for cases that become critical during the waiting period, and for cases in which an organ donor is urgently needed.
   (c) CORRECT.

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Lung Retransplantation

Xingan Wang

Glossary

Chronic lung allograft dysfunction (CLAD)	A persistent, irreversible decline in lung function, causing significant morbidity, and accounts for 40–50% of all death beyond the first year of lung transplantation [1, 2].
Bronchiolitis obliterans syndrome (BOS)	The earliest defined and the most common type of CLAD, featured by progressive obstructive dysfunction of lung allograft on spirometry, air trapping on chest computer tomography (CT) scan, and obliteration and fibrosis of small airways on histology [1].
Restrictive chronic lung allograft dysfunction (rCLAD)	Another phenotype of CLAD, featured by a restrictive pattern on pulmonary function testing, chest CT scan and histology [2].
Primary graft dysfunction (PGD)	One of the most important and common complications of lung transplantation, clinically characterized by diffuse alveolar infiltrates on chest X-ray imaging and hypoxemia, and strongly linked to both early mortality and late outcomes, including BOS [3].
Extracorporeal membrane oxygenation (ECMO)	A category of life support system that circulates the blood through an oxygenating system to support patients with severe gas exchange impairment [4].

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Key Points

- Lung retransplanation is a salvage procedure for irreversible failure of lung allograft(s) and/or the contralateral native lung retained at previous single lung transplantation in well-selected patients.
- The overall outcome of lung retransplantation is inferior to that of primary lung transplantation.
- The survival rates of retransplantation in well-selected patients with BOS approach that of primary lung transplantation, but the outcomes are poor in those candidates with rCLAD, PGD and acute rejection within one year of the initial lung transplant.
- In addition to the general criteria for lung transplantation, the factors to be considered in selecting retransplant candidates also include the inter-transplant interval, the cause of allograft failure, the previous transplant procedure, the need for ECMO, the recipient age and other comorbidities.

Lung retransplantation, also known as repeat transplantation, is lung transplant (LTx) in patients who had previously undergone single or bilateral lung transplantation (BLT), or LTx in combination with another solid organ, or those with a retransplant diagnosis [5, 6]. Ipsilateral, bilateral or contralateral procedures can be conducted to replace the irreversibly failed lung allograft(s) and/or the contralateral native lung retained at the initial single lung transplantation (SLT). According to the Thoracic Organ Transplant (TTX) registry data of the International Society for Heart and Lung Transplantation (ISHLT), the annual number of lung retransplants performed across the world steadily increased from 30 in 1990 to about 180 in 2016, accounting for around 4% of all LTx in the same year [5, 7]. The most common indication is advanced bronchiolitis obliterans syndrome (BOS), making up about 61.5% (691/1123) of the adult patients retransplanted for lung allograft failure during 1995–2013 [6]. Lung retransplanation also has been performed to rescue patients from severe primary graft dysfunction (PGD), acute rejection and other less common causes.

The overall outcome of lung retransplantation is inferior to that of primary LTx. Firstly, the retransplant recipients have lower survival rates than the primary lung recipients [6, 8]. According to the ISHLT registry data on adult recipients between January 1990 and June 2012, the median survival after lung retransplantation (n = 1,673) was 2.5 years, with unadjusted survival rates of 77% at 3 months, 64% at 1 year, 46% at 3 years, 37% at 5 years and 20% at 10 years [6]. In the same period, the median survival for primary LTx (n = 41,767) was 5.7 years, with unadjusted survival rates of 88% at 3 months, 80% at 1 year, 65% at 3 years, 53% at 5 years and 32% at 10 years. For the recipients who were alive one-year after retransplantation, the conditional survival rates were 6.3 years for retransplants and 7.9 years for primary recipients. Similar results were reported in a study based on 582 lung retransplants in the registry data of the United Network for Organ Sharing (UNOS) in the United States from 2004 to 2013 [9]. Secondly, the incidences of some complications are higher in the retransplant recipients than in the primary lung recipients. The ISHLT data during 1994–2013 showed that the cumulative incidences of BOS were 16.7% versus 9.2% within 1 year, and 53.4% versus 40.3% within 5 years after lung retranslantion versus primary LTx [6]. Consequently, bronchiolitis is a much more predominant cause of death in the retransplants than in the primary lung recipients. In addition, lung retransplantation is also associated with higher rates of hypertension (58.1% vs. 51.5%) and renal dysfunction (27.2% vs. 22.9%) at 1-year post-retransplant despite same immunosuppressive medications [6]. No significant difference was found between lung retransplants and primary LTx in the rates of acute rejection, hyperlipidemia, diabetes and other morbidities.

The selection criteria for retransplantation are essentially adopted from those for primary LTx. However, lung retransplantation is technically challenging and is associated with a more

complex postoperative course than primary LTx [10]. Factors contributing to a worse outcome should be considered in selecting candidates for retransplantation.

Complications following lung retransplantation relate to the inter-transplant interval and the causes of allograft failure. Almost 1 in 5 adult lung retransplants occurred within the first year of the previous transplant [7]. Severe PGD is the major cause of early allograft failure and the most common indication for retransplants within 1 month. Retransplants for acute rejection often occurred within the first year after the initial transplant, which accounted for approximately 3% of all lung retransplants [10, 11]. Worse survival after earlier retransplants have been consistently reported in both single- and multi-center studies since the early era of LTx [6, 9, 12–14]. For retransplants within 1 month or between 1 month and 1 year after primary LTx, the unadjusted survivals were about 40% or 55% at 1 year, 28% or 40% at 3 years, 24% or 35% at 5 years respectively, which are lower than the average survival rates for all lung retransplants in the 1990–2012 ISHLT registry data [6]. Retransplants for uncommon causes including bronchial dehiscence, acute organizing pneumonia, herniation of the heart, discovery of primary malignancies in the donor, etc. are met with mixed results [10, 15–19]. BOS is the predominant indication for retransplants beyond 1 year of the initial LTx. BOS continues to affect approximately 10% of patients each year, with the annual incidence highest in the first 5 years after transplant [5, 6]. In a single-center study reported in 2008, Aigner and colleagues reported that 30-day, 1-year and 5-year survival rates after retransplantation were 52.2%, 34.8% and 29.0% in the PGD group (n = 23), and 89.2%, 72.5% and 61.3% in the BOS group (n = 19), respectively [15]. Other single- and multi-center studies also confirmed that the survival rates of retransplants for BOS were similar to that of primary lung recipients [11, 15, 20–25]. BOS is the earliest defined and the most common type of chronic lung allograft dysfunction (CLAD), characterized by progressive obstructive dysfunction of the lung allograft on spirometry and air trapping on chest computer tomography (CT) scan [1, 5]. The histopathology of BOS is obliteration and fibrosis of small airways, namely, obliterative bronchiolitis (OB). By contrast, restrictive CLAD (rCLAD), represents a restrictive rather than obstructive pattern on pulmonary function testing, chest CT scan and histology [2]. The outcome was significantly worse in retransplants for rCLAD than for BOS. In a multi-center study reported by four European and North American centers, 94 patients undergoing retransplant for BOS were compared with 49 retransplants for rCLAD between 2003 and 2013. The median survival of retransplants for rCLAD was only 1.7 years, whereas the median survival after retransplant for BOS was 5.3 years which was comparable to ISHLT data for median survival rate of 5.7 years after primary LTx [6, 20]. Patients who underwent retransplantation for rCLAD redeveloped CLAD earlier and were more likely to redevelop rCLAD [20]. In a single center study on 87 retransplants conducted during 1995–2014, retransplants for BOS had longer median survival than for rCLAD (2.7 years vs. 0.9 years; p = 0.055) [13]. The outcome of lung retransplantation is good for bronchial anastomotic stenosis [10, 15, 16].

Extracorporeal membrane oxygenation (ECMO) can be used to bridge respiratory failure patients to LTx. However, the use of ECMO bridging is associated with poorer survivals in both primary and repeat LTx, but worse in the retransplants. According to an analysis on 15,772 lung recipients registered in the United Network for Organ Sharing (UNOS) database from 2001 to 2012, the 1-year survival rates for recipients with or without ECMO were approximately 60% (n = 156) versus 80% (n = 15,035) in primary LTx and 24% (n = 33) versus 64% (n = 548) in lung retransplants [26]. The 1-month survival rates were 67.3% versus 91.2% (p = 0.0002) in ECMO retransplants (n = 55) and non-ECMO retransplants (n = 799), based on data from the Scientific Registry of Transplant Recipients (SRTR) between 1988 and 2012 [27]. The poor outcome might be attributed to the morbidity of retransplant

candidates and the deficiency of ECMO. In the above mentioned SRTR study, the retransplant candidates with ECMO had higher body mass index (obesity), longer mechanical ventilation and hospitalization in the intensive care unit, and a shorter waitlist time before retransplantation than those without ECMO [27]. Even without ECMO, patients who were ventilator-dependent before retransplantation had a significantly worse outcome [9, 12]. Meanwhile, ECMO itself has adverse impact. In the era of 1970s–1980s, ECMO demonstrated little benefit beyond conventional treatment of respiratory failure in adults [4]. With the significant advances in ECMO technology and strategy, the risk-benefit profile has improved substantially. Influenced by the concept of awake bridging and ambulation, classical ECMO is moving toward downsized ECMO and portable extracorporeal gas exchange devices. Extracorporeal carbon dioxide removal ($ECCO_2R$) aims to facilitate ultra lung-protective ventilation in patients with less severe respiratory failure. Compared to classical ECMO, $ECCO_2R$ can be achieved with smaller cannulas at lower blood flow rates than are required for oxygenation [4]. In a meta-analysis of 21 patients bridged to retransplantation, 1-year survival reached 67% in the group with awake $ECCO_2R$/venovenous ECMO support and inter-transplant interval >2 years [28]. The other advanced ECMO support includes pumpless Novalung (Xenios, Germany), Hemolung (ALung Technologies, USA) and single dual-lumen cannula venovenous ECMO [4, 29]. A single-center analysis on 1111 lung recipients between 2006 and 2016 showed the median survivals were 1.25 year and 5 years in patients undergoing ECMO bridge to retransplantation (n = 11) compared with ECMO bridge to first LTx (n = 60), respectively [29]. ECMO bridge to primary LTx seems to have good short- and long-term outcomes in centers sufficiently experienced with ECMO and transplantation, but the outcome of ECMO bridge to retransplants remains very poor.

The era is also a major factor that affects lung retransplants more than primary LTx. The ISHLT registry data showed improving median survivals from 1.0 to 1.9 to 3.0 years for the periods of 1990–1997, 1998–2004, and 2005–2012 [6]. Notably, survival of retransplants in the latest era remained significantly worse than that of primary transplants in the earliest era, 3.0 years versus 4.3 years [6]. Single- and multi-center studies reported similar trends [9, 14, 30]. The impact of era mainly comes from the conceptual evolution of LTx and the changes of donor lung allocation policy. The most important conceptual transition over the last two decades is that BLT replaced SLT as the preferred procedure due to superior survival benefit. Consequently, the annual number of BLT worldwide steadily increased from <500 in the early 1990s to >3,500 in 2016, whereas the number of SLT has remained at 500–1,000 per annum [5]. The demand for contralateral retransplantation was directly affected because the criteria for initial SLT is tightened dramatically. The indirect effect is bilateral procedure would be preferred over ipsilateral or contralateral procedure when lung retransplantation is considered, although it is not as soundly based as in primary LTx. According to an analysis on 325 retransplants after an initial single lung transplant in the Organ Procurement and Transplantation Network database (OPTN, 1994–2012), survival was significantly worse in 50 ipsilateral than in 175 contralateral and 100 bilateral lung retransplants [30]. Another study based on UNOS data between 2004 and 2013 (n = 582) also suggested lower survival in single than in bilateral lung retransplants [9]. However, an analysis on UNOS registry data between 2005 and 2013 showed no significant difference in graft survival between recipients of single or bilateral lung retransplants when stratified by previous transplant type: single then single (n = 110), bilateral then single (n = 73), bilateral then bilateral (n = 184), and single then bilateral (n = 43), respectively [31]. This discrepancy may be partially attributed to the changing era effect. In a single-center study on 15 retransplants between 1988 and 2002, the retained graft was the initial site of the fatal infection in 4 of 6 patients who died from infection, and the origin of the sputum in two other patients who experienced disabling

chronic purulent expectoration [21]. Single procedure used to be the top choice, mainly due to the scarcity of lung donors [32]. In the recent era, bilateral retransplantation would be performed if there is any concern on the retained graft. As BLT becomes more common in both primary and repeat LTx, the outcomes are also improved in contralateral and ipsilateral retransplants due to more stringent criteria. The most influential policy adjustment is the introduction of the lung allocation score (LAS) in the United States and some other countries since 2005. The LAS system is a numerical value from 0 to 100, aiming to balance fairness and efficiency in the context of donor lung shortage. Compared to the "first-come, first-served" method, the LAS gives more priority to candidates for retransplantation. With the decreased waiting time, the number of retransplants has doubled and the outcome improved further since the implementation of the LAS [9, 16, 22].

The recipient age is independently associated with the outcome of lung retransplantation. Median survival of lung retransplants was 2.6 years for the age group of 18–34 years, 2.8 years for those of 35–49 years, 2.6 years for those of 50–59 years and 1.7 years for those older than 60 years during the period of 1990–2012 [6]. As for those younger than 18 years of age at the time of retransplant, median survival was about 2 years. According to the ISHLT Thoracic Organ Transplant (TTX) Registry Data, survival in children (n = 147) was inferior to that in adults (n = 2,280) within three years after the first time of retransplantation, although there was no significant difference in the overall survival during January 1990 and June 2016 [7]. About 75% of pediatric retransplants were carried out in children at 11–17 years of age, and half of them with a diagnosis of BOS [7, 33, 34]. Just like adult retransplants, 1-year survival for pediatric retransplants undertaken within one year after the primary LTx was significantly inferior compared with that of retransplants done beyond 1 year after the primary LTx [34]. Pediatric retransplantation was not well-investigated due to the small number of patients and events. The annual global volume of pediatric lung retransplants fluctuated between 2 and 10 per annum, accounting for 2–14% of all pediatric LTx [7, 33, 34].

The above-mentioned risk factors are not all. With the increase in lung retransplantation, risk factors will be studied more comprehensively. The outcome of lung retransplantation will likely improve further over the coming years.

Self-study

1. Which one of the followings is the best indication for lung retransplantation?
   (a) Acute rejection
   (b) Bronchiolitis obliterans syndrome (BOS)
   (c) Primary graft dysfunction (PGD)
   (d) Restrictive chronic lung allograft dysfunction (rCLAD)
2. Which factor would contribute to a more favorable outcome?
   (a) Ambulatory status before retransplantation
   (b) An institution without experience of retransplantation
   (c) Retransplant candidate older than 50 years of age
   (d) Retransplantation within the first 30 days after initial lung transplantation

Answers

1. Which one of the followings is the best indication for lung retransplantation?
   (a) Acute rejection
   (b) Bronchiolitis obliterans syndrome (BOS) CORRECT
   (c) Primary graft dysfunction (PGD)
   (d) Restrictive chronic lung allograft dysfunction (rCLAD)
2. Which factor would contribute to a more favorable outcome?
   (a) Ambulatory status before retransplantation CORRECT
   (b) An institution without experience of retransplantation
   (c) Retransplant candidate older than 50 years of age
   (d) Retransplantation within the first 30 days after initial lung transplantation.

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Single Versus Bilateral Lung Transplantation

Brian C. Keller and Bryan A. Whitson

Key Points

- Lung transplant outcomes continue to improve despite the transplantation of older and sicker patients.
- Long-term survival after bilateral lung transplantation now exceeds that of single lung transplantation.
- The choice of bilateral or single lung transplantation has economic and societal effects in terms of cost and distribution of organs.
- The decision to perform bilateral or single lung transplantation in a particular patient is patient-specific and should include factors such as the indication for transplant, recipient physiologic condition, urgency for transplant, and transplant center experience with each surgical procedure.

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Introduction

One of the longest running controversies in lung transplantation (LT) is the issue of single lung transplantation (SLT) versus bilateral sequential lung transplantation (BLT). Over the past 25 years, there have been many studies examining this issue, and to date, debate remains as to the optimal procedure for certain transplant indications. Undoubtedly, a one-size-fits-all approach will not work in every possible scenario, and therefore, patient-specific factors, scientific evidence, and the transplant team's experience and expertise with SLT (Fig. 1) versus BLT (Fig. 2) must all be considered when deciding the optimal type of transplant to offer a patient. For suppurative lung diseases like cystic fibrosis and bronchiectasis, BLT is the accepted approach due to risk of the infected native lung contaminating the transplanted allograft. For all other lung diseases, both SLT and BLT have been utilized over the years, though it has been difficult to clearly delineate the superiority of one approach over the other. In a perfect world, a prospective, randomized controlled trial is conducted, but this is not a feasible option. In this chapter, we review the evolution of the literature on SLT versus BLT, including post-transplant survival, quality of life, and societal effects, and we explore factors that could impact outcomes from each type of transplant.

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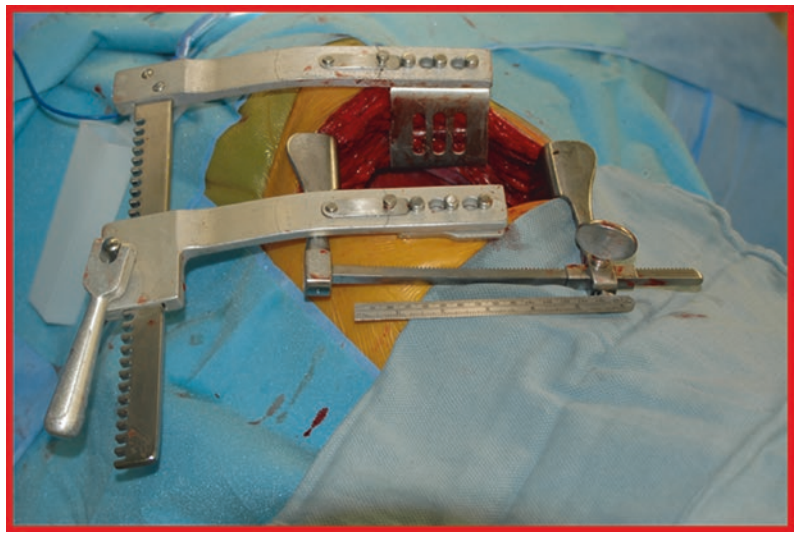

Fig. 1 Single lung transplant via thoracotomy

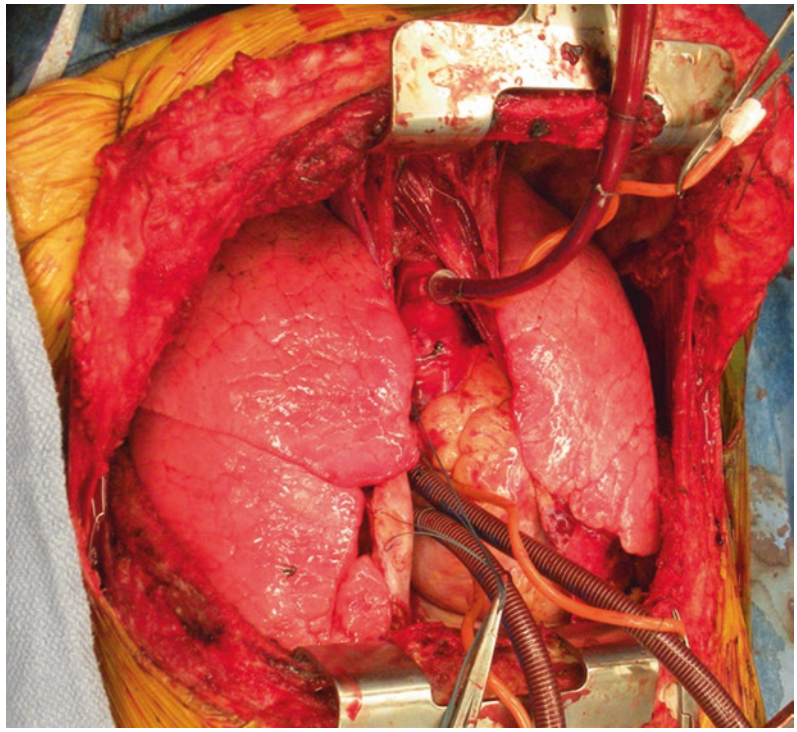

Fig. 2 Bilateral lung transplant via thoracosternotomy with central cannulation for cardiopulmonary bypass

The art and science of LT has evolved significantly over the past 30 years. Improvements in surgical technique have enhanced early LT survival, while modifications to immunosuppressive regimens have been slower to evolve. A shift in the demographics of patients undergoing LT has also occurred with the implementation of the Lung Allocation Score (LAS) in the United

States in 2005. Prior to the LAS, time on the waitlist was the major factor influencing likelihood of receiving a life-saving transplant. Under this system, patients with slower progressing diseases such as chronic obstructive pulmonary disease (COPD), were more likely to receive a transplant due to their lower waitlist mortality. With the introduction of the LAS, emphasis shifted to disease severity and risk of death while awaiting transplant, leading to the transplantation of older and sicker patients in today's practice. Despite, this shift in patient demographics, survival after LT has continued to improve, albeit slowly, from a median survival of 4.8 years in 2005 to 6.2 years in 2018 [1, 2]. Survival after SLT or BLT has also increased over this same period, but to different degrees with longer survival observed with BLT (SLT median survival 4.3 and 4.7 years and BLT median survival 5.6 years and 7.6 years in 2005 and 2018, respectively). This discrepancy is even more apparent when considering long term survival conditional on survival at least 1 year. In this case, SLT conditional median survival only increased from 6.3 to 6.5 years, whereas BLT conditional median survival increased from 8.5 to 10.0 years [1, 2]. These data provide an important background when evaluating the scientific literature on SLT versus BLT outcomes, as data has vacillated regularly over the past 20 years.

Post-transplant Survival

When evaluating survival after SLT versus BLT, it is important to consider both early and long-term survival. Early registry studies from the pre-LAS period reported lower 30-day mortality associated with SLT in both interstitial lung disease and COPD [3, 4], while smaller single institution studies failed to identify significant differences in early outcomes between SLT and BLT [5, 6]. Larger, more recent studies have failed to identify differences in early mortality between SLT and BLT [2, 7]. The discrepancy between older and more recent studies regarding early survival after LT can probably be explained by an 'experience effect'. For most institutions, BLT was adopted later as an option, and therefore, institutional and surgeon experience with this procedure was delayed. As surgeons and institutions gained experience, the differences in early survival between SLT and BLT disappeared.

Long-term outcomes between SLT and BLT are more clearly defined. As described previously, median survival following SLT significantly lags behind that of BLT in the International Society for Heart & Lung Transplantation (ISHLT) International Thoracic Organ Transplant Registry, a registry of data reported annually for the past 17 years (Fig. 3).

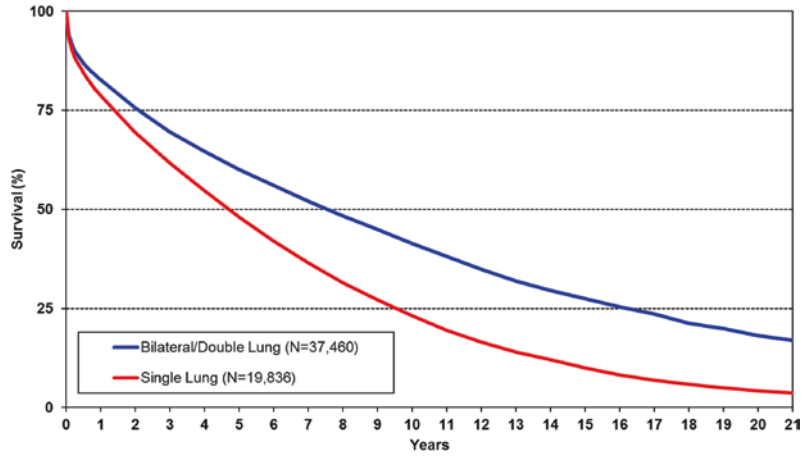

Fig. 3 Adult lung transplant Kaplan-Meier survival by procedure type for primary lung transplantation. Graph provided courtesy of the ISHLT Thoracic Organ Transplant Registry [2]

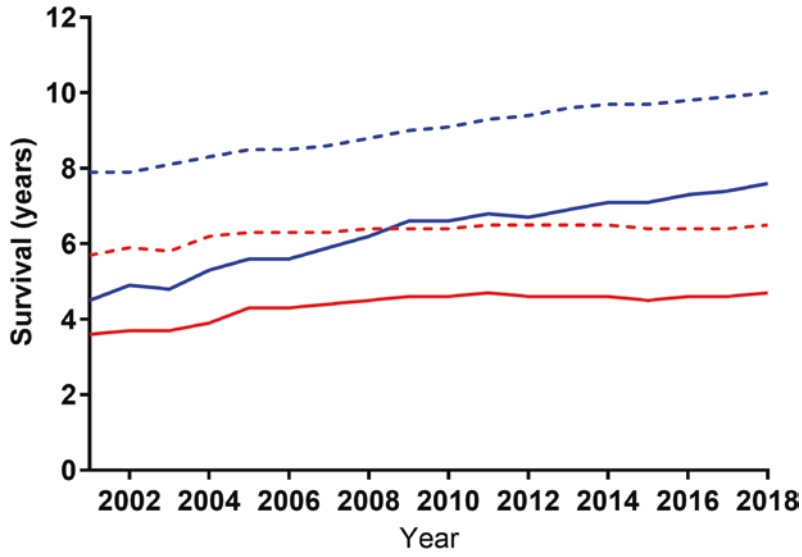

Fig. 4 Annual median survival of lung transplant recipients. Survival data from ISHLT Thoracic Organ Transplant Registry annual reports from 2001 to 2018 were used to construct the figure. Solid lines represent total annual median survival while dotted lines represent annual median survival conditional on survival 1 year after transplant (SLT = red, BLT = blue)

Over this time, long-term median survival after SLT plateaued at 4.6 years in 2005 (Fig. 4, solid red line), an improvement of only 1 year compared to 2001 levels, while BLT median survival continued to improve to its current level of 7.6 years, up from 4.5 years in 2001 Fig. 4, solid blue line) [2]. Long-term survival conditional on survival at 1 year post-transplant, while increased overall, mirrors these trends (Fig. 4, dotted lines). Several other large studies have consistently demonstrated long-term survival benefits for BLT over SLT. Washington University in Saint Louis recently published its single-center experience in 1500 lung transplant recipients from 1988 to 2016 and demonstrated longer survival after BLT than SLT at 1 year, 3 years, 5 years, 10 years and 15 years [8]. Incidentally, outcomes from the pre-LAS and post-LAS periods were also compared in this high volume single institution, and improved survival was noted in the post-LAS period despite performing more BLT procedures in an older, sicker patient population [8]. In a Swedish single-center study, BLT recipients had higher survival at all times from 5 years to 20 years post-transplant [9], again supporting the long-term benefit of BLT over SLT, and this BLT benefit was particularly notable in LT candidates with higher LAS scores [10].

The long-term survival benefit of BLT over SLT holds when considering specific indications for lung transplant. In idiopathic pulmonary fibrosis (IPF), ten Klooster et al. published a retrospective analysis of all lung transplants done for IPF from 1989 to 2011 in the Netherlands. BLT recipients in the 3 Dutch transplant centers had nearly double the survival compared to SLT recipients (median 10 years vs. 5.5 years) [11]. Similar findings were observed in the U.S. by Force et al. using the United Network for Organ Sharing (UNOS) database of LT performed for pulmonary fibrosis from 1987 to 2008. Of patients surviving at least 1 year, BLT recipients lived significantly longer than SLT recipients (12.08 years vs. 6.8 years) [12]. Following on these results, another analysis of the UNOS database, this time from 2005 to 2012, showed significantly longer graft survival in IPF patients after BLT than SLT (70.7 months vs. 48.9 months) [7]. When controlled for confounding variables, the findings persisted.

In COPD, there remains some controversy regarding the impact of SLT and BLT. An early version of the UNOS database was used to examine LT performed from 1991 to 1997. In this first analysis of SLT versus BLT in COPD, BLT was associated with better outcomes in patients less than 50 years of age. Equivalent outcomes between SLT and BLT were found in patients between 50 and 60 years, while those patients older than 60 years did better with SLT [3]. It should be noted, though, that 5 year outcomes were not able to be calculated for patients over 60 years using the dataset from this early period of LT, whereas patients over 60 years routinely live 5 years in the current LT era [1, 2, 13]. Consistent with the 'experience effect', later studies, both single institution and registry analyses, failed to identify superiority of SLT over BLT in COPD. Borro and colleagues reported on 280 LT recipients at a Spanish center and found no difference in survival by transplant type in COPD patients [14]. In contrast to their results describing a benefit of BLT over SLT in IPF patients in the UNOS database, Schaffer et al. found no difference in 5 year survival among COPD patients undergoing SLT or BLT [7]. However, despite the lack of statistical difference in their dataset at 5 years post-transplant, the authors hypothesized that the impact of BLT may be both "statistically and clinically significant at 10 years" [7]. Crawford et al. repeated Shaffer's study, but utilized 2 more years of UNOS data (2005–2014 instead of 2002–2012). The inclusion of 2 additional years' worth of data increased the total number of COPD transplant patients with follow-up data at 5 years from 510 to 1030. With this larger dataset, the impact of BLT on survival in COPD patients at 5 years post-transplant was then shown to be significantly better than SLT (59% vs. 51% survival for BLT and SLT, respectively) [15]. The ISHLT Registry data has consistently reported improved survival for BLT in COPD compared to SLT, and in the most recent Registry iteration, survival at 5 years post-transplant was 60% for BLT and 50% for SLT [2]. Taken together, the data clearly supports a long-term survival benefit of BLT over SLT in COPD. Furthermore, the once significant early post-transplant mortality data in favor of SLT from older eras of LT is no longer discernible from early BLT transplant outcomes.

Post-transplant Lung Function

While survival after LT is certainly an important metric, it is not the only factor to consider when deciding on type of transplant to perform. As expected, BLT provides for larger post-transplant overall lung capacity than SLT. This is noted by higher forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) in BLT recipients compared to SLT recipients [16]. However, the lung capacity ratio between BLT and SLT is less than 2:1 due to some contribution from the remaining native lung in SLT recipients. Over time, lung function remains more stable in BLT than SLT recipients, possibly due to more rapid decline in function of the native diseased lung in SLT recipients [16] or to higher rates of bronchiolitis obliterans syndrome (BOS) rates in SLT compared to BLT [17]. Diffusing capacity for carbon monoxide is similar between SLT and BLT one year after transplant [18].

Post-transplant and Quality of Life and Functionality

In addition to quantity of life, health-related quality of life (HRQOL) is, in some cases, as important or more important, to the potential LT recipient. Compared to survival outcomes, there have been notably fewer studies evaluating the effect of SLT and BLT on post-transplant QOL. It is well established that LT, in general, provides an improvement in HRQOL compared to those with end-stage lung disease who do not receive a transplant (reviewed in [19]). In the first 2 years after transplant there is no difference in HRQOL between SLT and BLT patients [17, 20]. However, between 2 and 3 years, SLT recipients develop a more precipitous decline in their annualized HRQOL compared to BLT, such that by 5 years post-transplant, SLT recipients have a HRQOL

below that of the general population average. While BLT recipients also exhibit a decline in HRQOL over time, this decline is much slower and remains within range of the general population for up to 10 years after transplant [20].

Following LT, all patients exhibit an early decline in strength and exercise capacity, that with the help of pulmonary rehabilitation programs, improves over time [21]. This post-transplant weakness appears to be more a function of pre-transplant deconditioning related to chronic end-stage lung disease than to the type of transplant procedure performed. Large studies comparing SLT and BLT recipients in terms of post-transplant strength and conditioning are lacking, but two small, single-center studies found no difference in maximal exercise capacity and peripheral muscle strength between recipients of SLT or BLT [18, 22].

Allograft Rejection

Following LT, acute or chronic allograft rejection may develop and impact survival and quality of life. Acute cellular rejection (ACR) usually develops within the first year after transplant and has been linked to later BOS development. To date, studies have failed to identify differences in the incidence of ACR between recipients of SLT and BLT [14, 17, 23].

BOS is a form of chronic lung allograft dysfunction (CLAD) that is progressive in nature and without curative therapy. Compared to the data with ACR, whether BOS is linked or not to SLT or BLT is less clear. In a small single-center retrospective study of 73 patients with emphysema, Borro et al. found no difference in the occurrence of BOS between those patients who received SLT versus BLT [14]. More recently Fakhro et al. reviewed 278 patients who received lung transplants for various indications at Lund University in Sweden. Again, no difference in the incidence of BOS (grade ≥ 2) was found between SLT and DLT. In contrast to these studies, other single-center studies have reported increased incidence of BOS following SLT compared to BLT. Cassivi et al. reported on the early Washington University experience [24], while Hadjiliadis et al. presented the early Duke University experience [25]. Both studies demonstrated reduced BOS-free survival in SLT compared to BLT with separation of the Kaplan-Meier BOS-free survival curves beginning between years 1 and 2 post-transplant and widening thereafter. Consistent with these reports, smaller institutional studies have also found higher rates of BOS and reduced BOS-free survival in SLT recipients [17, 23]. Whether or not there exists a definitive difference in BOS incidence between SLT and BLT, BLT patients may be better equipped to handle the development of BOS. In Fakhro's study that found no difference in BOS incidence, BLT patients survived longer following development of BOS than did SLT patients, perhaps as a result of their greater pulmonary reserve as described above [9].

Economic and Societal Effects

What has been discussed to this point, has focused on effects on the individual patient. However, in LT, as in other solid organ transplants, there remains a scarcity of donors available for potential transplant candidates. Therefore it is prudent to consider the economic and societal impacts of transplanting two lungs into a single recipient or splitting donor lungs for two separate recipients as in SLT. The largest study to date to evaluate the economics of LT was a seven center study out of the U.K. in 2002 that evaluated the costs associated with SLT and BLT over a 4 year period from 1995 to 1999 [26]. Lung transplant, in general, had higher mean estimated costs than medical treatment of end-stage lung disease ($176,640 and $180,528 for SLT and BLT, respectively, compared to $73,564 for medical treatment alone). The higher costs were driven, however, by increased survival following LT compared to not receiving a LT and by predicted longer survival from BLT over SLT in the model. On a cost per quality-adjusted life-year gained basis, BLT was favored over SLT ($32,803 for BLT, $48,241 for SLT), even in this early era of BLT.

In terms of societal impact of SLT and BLT, it is not surprising that studies consistently find that more candidates receive LT and waitlist deaths are predicted to be lower with higher utilization of SLT than BLT [27]. However, factors such as waitlist size, donor availability, and geographical location can influence these outcomes, and not all donors are able to donate both lungs due to factors such as trauma, infection, and aspiration. Donor availability has long-been a limiting issue in LT with high variability based on local and regional factors. Attempts to increase the donor pool have included the use of extended-criteria donors (reviewed in [28]), donation after circulatory death, ex vivo lung perfusion for marginal quality donors, efforts to improve donor management (reviewed in [29]), and efforts to increase organ donor registrations [30, 31]. In the future, utilization of Hepatitis C virus positive donors [32] and bioengineered lungs [33] could further mitigate the lung donor shortage, thereby reducing the societal impact of SLT over BLT.

Unique Situations

Despite the evolution in the field of LT and the data supporting the long-term benefits of BLT over SLT, a one-size-fits-all approach is not always feasible due to the high heterogeneity of potential LT candidates and the availability of lungs suitable for transplant. In particular, certain situations have been shown to be unique in the SLT versus BLT debate. For example, COPD patients with secondary pulmonary hypertension had worse outcomes after BLT than SLT in a review of UNOS registry data [34], while obese patients with body mass index > 30 kg/m^2 had worse 90 day mortality with BLT [35]. Further, frail recipients or recipients at the extremes of age may not tolerate BLT as well as SLT, though transplant center experience is likely to play a significant part in these findings as data from earlier eras noted worse outcomes in patients over age 60 after BLT [3], whereas more recent data show no difference in survival between BLT and SLT in this age group [36]. As time has passed, older and sicker recipients have undergone transplant with continual improvement in overall LT outcomes, consistent with the 'experience effect' [2], suggesting that BLT can safely be performed with good outcomes in the older population.

Summary

Over the past 30 years, LT outcomes have slowly and steadily improved despite the transplantation of older and sicker patients. When deciding whether to perform a SLT or BLT for a given patient, the transplant team should consider a variety of factors, including expected outcomes for each procedure based on the most recent and comprehensive data, the team's expertise with BLT and SLT, recipient-specific factors that may influence outcomes from each procedure, and local/regional factors that might influence time on the waiting list and likelihood of receiving a transplant. As transplant centers have gained experience over the past 3 decades, improvements in long-term survival after BLT have outpaced that of SLT which plateaued around 2005. This effect is observed despite the introduction of the LAS and a higher rate of transplant in sicker patients. While the number of potential recipients still dwarfs available donors, many mechanisms have been implemented to address this ongoing need. The goal of LT is to provide appropriate end-stage lung disease patients with an improved quality and quantity of life for as long as possible. With this in mind, strong consideration should be given to performing BLT whenever possible based on the most recent data, while acknowledging that unique situations may necessitate the use of SLT.

Self-study

1. For which of the following lung diseases, are only a bilateral lung transplant an option:
   A. COPD
   B. Cystic fibrosis
   C. IPF/ILD
   D. Pulmonary hypertension
   E. A and B
   F. B and D

2. For which surgical approach is cardiopulmonary bypass or extracorporeal life support required for transplantation:
   A. Bilateral lung transplant via sequential thoracotomies
   B. Bilateral lung transplant via sternotomy
   C. Bilateral lung transplant via thoracosternotomy
   D. Left single lung transplant via sternotomy
   E. Single lung transplant via thoracotomy
   F. A and B
   G. B and D

Answers

1. F, responses both B and D. Cystic fibrosis, a suppurative lung disease, and pulmonary hypertension in general require bilateral lung transplantation.
2. G, responses both B and D. Sternotomy approach to left lung transplant necessitates mechanical circulatory support. Occasionally a right lung transplant may be performed via sternotomy without support though this would be rare.

Compliance with Ethical Requirements

Consent for Publication All authors provide Springer with consent to publish this work.

Conflict of Interest Dr. Keller declares that he receives research support from Therakos.

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Informed Consent Not applicable.

Animal Studies No animal or human studies were carried out by the authors for this article.

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The Role of Ex-vivo Lung Perfusion (EVLP) in Lung Transplantation

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Key Points

- EVLP allows for prolonged evaluation and reconditioning of marginal donor lungs that would have otherwise been discarded, thereby expanding the donor pool.
- EVLP permits for longer organ preservation time, allowing organs to travel further distances.
- Outcomes for transplanted lungs evaluated by EVLP are noninferior to lungs transplanted by standard criteria.
- The EVLP circuit can be used as a bioreactor to deliver targeted therapies with the potential to improve allograft function.

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Introduction

Lung transplantation (LTx) is the ultimate solution for patients with end stage lung disease. However, there is a severe shortage of donor lungs. As more patients are being listed for LTx, the waiting list mortality has been increasing (1). Despite improvements in donor management and organ preservation, only 15–20% of all cadaveric donor lungs are being retrieved and transplanted.

Advances in LTx now allow for more of the previously unutilized donor lungs to become suitable for transplantation. There is more liberal use of extra corporeal membrane oxygenation (ECMO) post-transplantation for marginal lungs (2). Donor lungs previously turned down due to uncertain function are used after assessment with ex-vivo lung perfusion (EVLP). EVLP may even ameliorate lung injury in some cases, as well as recondition the lung, and allow transplantation from donors previously deemed unsuitable (3).

EVLP utilizes components of cardiopulmonary bypass (CPB) and a ventilator to isolate the lung and evaluate its function outside of the body as a means of determining its suitability

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for transplant. Benefits of EVLP may include removal of excessive interstitial fluid, washing out of inflammatory mediators, and allowing for alveolar recruitment at low airway pressures. Thus, EVLP provides a platform for organ reconditioning which will allow some of the previously non-transplantable organs to meet criteria for transplantation.

History of EVLP

Ex-vivo perfusion is not a new concept and can be tracked back to 1812. The first ex-vivo organ perfusion was described by Carrel and Lindbergh (4) in 1935, when they explanted thyroid glands of cats and rabbits and perfused them. An ex-vivo isolated lung perfusion technique was prevalent in the 1950s for the application of chemotherapeutic agents. In 1970, Jirsch et al. introduced EVLP as a method to assess the quality of lung grafts during storage prior to transplantation using a canine model. Steen et al. in Sweden (5) developed a new method for ex-vivo lung assessment in the mid 1990s. In 2001, this technique led to the first reported successful case of using EVLP in human LTx from a non-heart-beating donor (6).

Rationale for EVLP and Indications for Its Use

The International Society for Heart and Lung Transplantation (ISHLT) lists the following criteria as the currently accepted "ideal" lung donor: age < 55 years, ABO compatible, clear chest radiograph, appropriate size match, PaO_2/FiO_2 (P/F ratio) > 300 on FiO_2 of 1.0 and positive end expiratory pressure (PEEP) of 5 cm H_2O, < 20 pack-year smoking history, absence of chest trauma, no evidence of aspiration/sepsis, no prior cardiopulmonary surgery, absence of organisms on sputum Gram stain, and clear bronchoscopy (7). Failure of donor lungs to meet criteria is largely due to events leading up to death which result in a poor organ.

EVLP allows for evaluation and reconditioning of extended donor criteria lungs and marginal lungs that require further assessment prior to transplantation. These high-risk lung donors must meet one of the following criteria: P/F ratio < 300 mmHg; pulmonary edema detected on the last donor chest radiograph; atelectasis and poor alveolar recruitment during procurement; blood transfusions exceeding 10 units; or donor after circulatory death (DCD) (8). EVLP should not be used if donor lungs have an established pneumonia or other active infection, severe mechanical lung contusions in more than one lobe, or gross gastric aspiration.

EVLP to Expand the Donor Pool

In 2001, Steen et al. were the first to use EVLP to successfully recondition and transplant a donor lung that was previously considered to be unsuitable for transplantation. These donor lungs were initially deemed unsuitable due to ongoing airway bleeding, bilateral contusions, and poor gas exchange. Reconditioning according to the Lund protocol led to improved gas exchange from $PaO_2 = 9$ kPa on FiO_2 0.7 to $PaO_2 = 52.2$ kPa on FiO_2 100% and subsequent transplantation [10]. Studies of EVLP have since focused on the reconditioning and utilization of marginal donor lungs.

Of the cadaveric donor with consent for lung donation, only 15–20% of lungs are actually used for transplantation. The rest are declined due to unfavorable donor history or complications of the donor lungs such as contusion, pulmonary edema, and aspiration [7]. For marginal donor lungs that would normally be discarded, EVLP offers a controlled environment to evaluate and distinguish between potentially reversible from irreversible injury for extended periods following their retrieval. One such group of donor lungs are those from hanging victims, which are typically not used for transplant due to injury sustained by forced inhalation against a closed glottis. In a small study of 5 sets of donor lungs, Bennett et al. demonstrated that 60% of

donor lungs from hanging victims were suitable for transplant after 3 hours of evaluation and conditioning with EVLP [1]. Extending preservation time without compromising outcomes is another potential benefit.

The first prospective, nonrandomized clinical trial for EVLP was the HELP trial published in 2011. Cypel and the Toronto group transplanted 20 out of 23 high-risk donor lungs after reconditioning the allografts with 4 hours of EVLP according to the Toronto protocol. Donor lungs were classified as high-risk if they had a $PaO_2/FiO_2 < 300$ mmHg, radiographic evidence of pulmonary edema without infection, poor lung deflation or inflation, blood transfusions exceeding 10 units, or donation after circulatory death. When compared to non-EVLP lungs transplanted during the same period, the EVLP group did not demonstrate significant differences in PGD, 30-day mortality, duration of post-operative ventilation, bronchial complications, or lengths of ICU or hospital stays [3]. Longer-term follow up of these recipients have shown significantly improved quality of life and noninferior functional outcomes such as FEV1, increase in 6-minute walk distance, or number of acute rejection episodes.

Since 2014, the Toronto group has reported a 30% increase in their LTx activity which they largely attribute to their use of EVLP [12]. Other centers have also expanded their transplant volume using the Toronto technique, with multiple groups reporting noninferior outcomes and a 25–30% increase in LTx performed within the first two years of starting an EVLP program. The success of EVLP in the utilization of marginal donor lungs has not been limited to the Toronto technique, as Wallinder et al. reported noninferior results transplanting marginal allografts that were reconditioned on the Vivoline LS1 (Vivoline Medical AB, Lund, Sweden) using the Lund protocol. Their midterm follow-up results demonstrated an 18% increase in LTx volume. Together these outcomes have demonstrated the ability of EVLP to safely expand the donor pool by increasing the utilization of marginal allografts.

EVLP Circuit

A typical EVLP circuit has two primary components: (1) a circuit that circulates, deoxygenates, and filters the perfusate that is circulated through the lung vasculature and (2) a ventilator that provides oxygenation to the lungs through the airways. The basic components of the EVLP circuit include the reservoir, centrifugal pump, gas exchange membrane and gas blender, leukocyte filter, and heat exchanger (Fig. 1).

Various physiological parameters in the lung allografts, such as perfusion flow rate, pulmonary artery pressure, and lung compliance, are continuously monitored during EVLP. The perfusate gas levels, which are equivalent to in vivo arterial blood gases, are used to evaluate the function and quality of the lung grafts. Thus, normothermic EVLP allows the evaluation of lung grafts by multiple criteria under conditions that mimic in vivo pulmonary physiological conditions.

EVLP Technique

Currently, there are three major EVLP protocols with different underlying rationales: the Lund protocol, the Toronto protocol, and a portable EVLP protocol. The differences in their settings and characteristics are attributed to their aim and strategy of using EVLP (Figs. 2 and 3).

EVLP Protocols

The Lund Protocol

The Lund protocol utilizes a cellular perfusate and full-flow target perfusion of 100% cardiac output. First, the perfusion circuit is primed with 2 L STEEN Solution™ (XVIVO Perfusion AB, Gothenburg, Sweden) supplemented with matched, washed, irradiated, and leukocyte-filtered erythrocyte concentrate to a hematocrit of 10–15%. STEEN Solution

Transmedics OCS (Organ Care System) **XVIVO Perfusion System (XPS)**

Fig. 1 EVLP systems

contains human serum albumin and dextran to maintain a high colloid osmotic pressure in the perfusate and prevent pulmonary edema.

The reconditioning phase beings with an initial perfusion flow of 50–100 ml/min, perfusion pressure ≤20 mmHg, and perfusate temperature of 25 °C. The perfusion flow is slowly increased to full cardiac output of 5–6 L/min while maintaining the perfusion pressure at ≤20 mmHg. The perfusate temperature is also gradually increased to 37 °C over 15 minutes. When the temperature reaches 32 °C, careful ventilation is started at 1 L/min. The rate of ventilation is increased by one liter per minute for every degree increase in temperature until normal ventilation of 100 ml/kg/min is reached. The ventilator settings include respiratory rate of 15–20 breaths/min, FiO_2 of 0.5, and PEEP of 5 cm H_2O [6].

During the evaluation phase, the gas exchanger fully deoxygenates the perfusate with 93% nitrogen and 7% CO_2 while the lungs are ventilated to assess their oxygenating capacity. The perfusion flow is maintained at 5–6 L/min during the evaluation phase. Venous and arterial perfusate samples are taken after exposure of 5 minutes each to FiO_2 of 0.21, 0.5, and 1.0. The endotracheal tube is briefly disconnected from the ventilator to perform the deflation test. A satisfactory deflation test results in global atelectasis of the lungs. Lungs are accepted for transplantation if they pass the deflation test, maintain a PaO_2 ≥50 kPa with FiO_2 of 1.0, and do not have macroscopic evidence of pulmonary infiltrates. The reconditioning and evaluation phases should take approximately 1–2 hours [6].

Once the lungs have been deemed suitable for transplant, they are cooled and preserved. The perfusate temperature is reduced to 25 °C, and perfusion is stopped altogether when the temperature stabilizes. The lungs are semi-inflated at a FiO_2 of 1.0, and the pulmonary artery cannula and trachea are

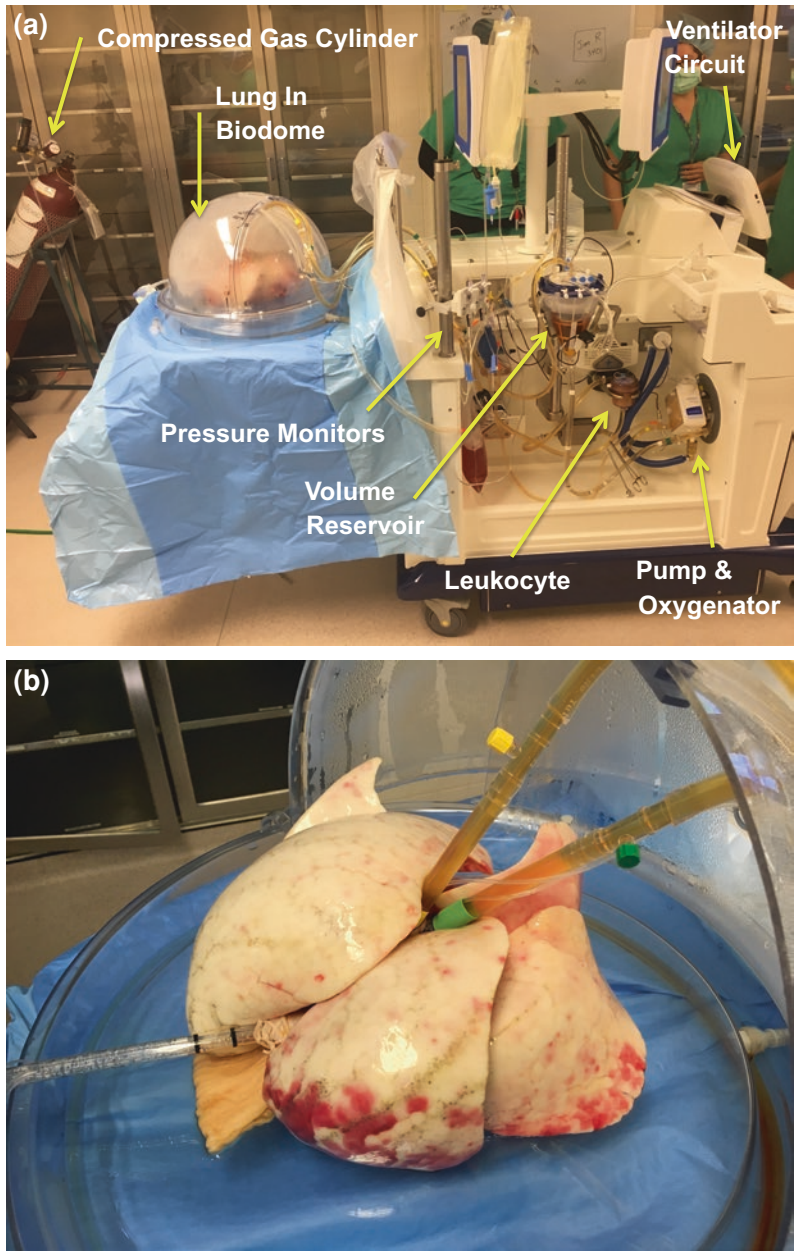

Fig. 2 **a** Components of an EVLP system. **b** Lung on EVLP

clamped. The lungs are immersed in perfusate with additional buffered Perfadex, and the system circulates and oxygenates the perfusate throughout the lung reconditioning box to preserve the lungs at 8 °C until transplantation [6].

The Toronto Protocol

The Toronto protocol developed by Cypel et al. is the most widely used protocol for EVLP [2]. The Toronto technique uses an acellular perfusate, a closed circuit with positive left atrial

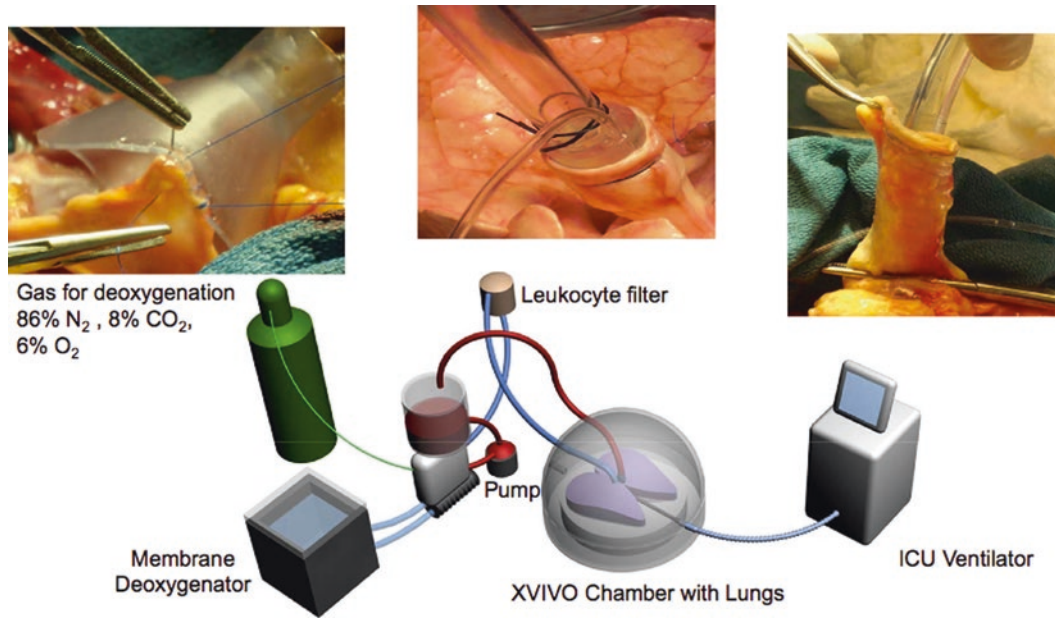

Fig. 3 EVLP cannulation and clinical circuit, courtesy of XVIVO

Table 1 Current protocols for EVLP

	Toronto	Lund	OCS™
Perfusate	Acellular; STEEN™ solution	Cellular; STEEN™ solution with RBCs to HCT 15%	Cellular; OCS™ lung solution with RBCs to HCT 15–25%
Target flow	40% CO; continuous	100% CO; continuous	Continuous monitoring mode: 2.5–3.0 L/min Preservation mode: 1.5–2.0 L/min Pulsatile
Time to 37 °C	30 minutes	15 minutes	15 minutes
Temperature in transit	Cold ischemic	Cold ischemic	Normothermic
Left atrium	Closed; 5 mmHg	Open; 0 mmHg	Open; 0 mmHg
Ventilation start temperature	32 °C	32 °C	34 °C
PEEP	5 cm H_2O	5 cm H_2O	Continuous monitoring mode: 5 cm H_2O Preservation mode: 7 cm H_2O
Tidal volume	6–8 ml/kg	5–7 ml/kg	6 ml/kg
Respiratory rate	7 breaths/min	15–20 breaths/min	12 breaths/min
FiO_2	21%	50%	Continuous monitoring mode: 21% Preservation mode: 12%
Perfusion time	4–6 hours	1–2 hours	Transport time

pressure (LAP), and a target perfusion flow rate of 40% of cardiac output. First, the circuit is primed with 1.5 L STEEN Solution™. The donor lungs are prepared for EVLP by sewing the left atrial (LA) cuff onto the funnel-shaped outflow cannula and the pulmonary artery (PA) onto the inflow cannula with 4-0 monofilament suture. Using a closed circuit with a sustained LAP of 5 mmHg was thought to prevent cyclical open-close injury to the pulmonary capillaries, and led to less pulmonary edema in large animal studies [5].

The first hour of EVLP involves initiation of perfusion and ventilation with a controlled, incremental increase in temperature to 37 °C. First, the circuit is de-aired with a slow retrograde flow through the LA cannula. The PA cannula is then connected to the circuit and antegrade flow is started at 150 ml/min at room temperature. The perfusate temperature is then slowly increased to 37 °C over 30 minutes. When the perfusate temperature reaches 32 °C, ventilation is started and gas flow through the gas-exchange membrane is initiated at 0.5 L/min to deoxygenate the inflow perfusate. The following protective ventilation settings are use during the maintenance phase of EVLP: tidal volume of 6–8 ml/kg; PEEP of 5 cm H_2O; respiratory rate of 7 breaths/min; FiO_2 of 0.21. Pulmonary artery wedge pressure is maintained at 25 cm H_2O through recruitment maneuvers. Left atrial pressure is maintained at 3 to 5 mmHg by adjusting the height of the hard-shell reservoir [2].

Lungs are assessed hourly while on the EVLP circuit for a minimum of four hours. Recruitment maneuvers are performed 10 minutes prior to measuring peak inspiratory pressure (PiP), plateau pressure (Pp), dynamic and static compliance, pulmonary vascular resistance (PVR), and gas exchange function. Arterial and venous perfusate gas analyses are also performed hourly, along with glucose and lactate levels. X-ray and bronchoscopy are performed at 1 hour and every subsequent 2 hours to assess atelectasis and pulmonary edema [8].

The decision to transplant is based on a measured $PaO_2/FiO_2 > 350$ for two consecutive hours in the absence of a 10% deterioration in PiP, Pp, PVR, and compliance. After the final ex-vivo evaluation, the lungs are cooled to 20 °C on the circuit, at which point perfusion and ventilation are stopped. The trachea is clamped to keep the lungs inflated, and the lungs are stored in Perfadex at 4 °C until transplantation [2].

The OCS™ Protocol (TransMedics FDA Protocol)

The Organ Care System (OCS™) Lung (TransMedics Inc., Andover, MA, USA) is the first portable normothermic organ perfusion system, on which organs are perfused with a cellular perfusate. Since the retrieved organ is perfused immediately following removal at the donor hospital and perfusion is maintained continuously during transport to recipient sites, the OCS minimizes cold ischemic time. By contrast, the Toronto and Lund protocols involve keeping the donor lungs in static cold storage in transit from procurement to the recipient hospital, thereby accrue longer cold ischemia times in comparison to the OCS.

First, the donor lungs are procured and instrumented for attachment to the OCS™ Lung System. The left atrium drains openly into the organ chamber of the circuit without positive pressure. Perfusion with the pulsatile pump is initiated at 1.5–2 L/min and 32 °C, and then increased to 37 °C over 15 minutes. When the temperature reaches 34 °C, ventilation is initiated using the OCS™ Lung System's integrated ventilator.

The ventilator settings and frequency of assessments depends on whether the ventilator is set to Bronchoscope Mode, Continuous Monitoring Mode, or Preservation Mode. It is recommended to initiate the first 5 minutes of ventilation in Bronchoscope Mode, during which the lungs are ventilated with room air ($FiO_2 = 0.21$) and bronchoscopic evaluation can be conducted as necessary. During this time, the lungs are wrapped in a sterile membrane to prevent over distension and the organ chamber is sealed.

The ventilator is then switched to Continuous Monitoring Mode, during which the

oxygenating capacity of the lungs is assessed. To simulate near physiologic perfusion, the lungs are ventilated with room air ($FiO_2 = 0.21$) as the perfusate is continuously deoxygenated by using the proprietary Lung Monitoring Gas (Transmedics, Andover, MA, USA) through the gas exchanger. During Continuous Monitoring Mode, ventilator settings include PEEP of 5 cm H_2O, tidal volume of 6 ml/kg of donor ideal bodyweight, and respiratory rate of 12 breaths/minute with a flow rate of 2.5–3.0 L/min. The Continuous Monitoring Mode lasts for 180 seconds, after which the system automatically reverts to Preservation Mode.

Preservation Mode involves the lung rebreathing the same captive breath of Lung Preservation Gas (Transmedics, Andover, MA, USA), allowing the system to conserve battery power and the lungs to conserve heat and humidity. Ventilator settings for Preservation Mode include PEEP of 7 cm H_2O, tidal volume of 6 ml/kg of donor ideal bodyweight, respiratory rate of 12 breaths/minute, and FiO_2 of 0.12 with a flow rate of 1.5–2.0 L/min. Lung Preservation Gas flows into the ventilation circuit at 300 ml/min to maintain proper gas concentration and PEEP. The system is typically set in Preservation Mode for organ transport.

The decision to implant EVLP-evaluated lungs is based on acceptable trends in pulmonary vascular resistance, peak airway pressure, and pulmonary artery pressure, as well as a P/F ratio $\geq$ 300 during a final assessment in Continuous Monitoring Mode. At the end of preservation, 3–5 L cold OCS™ Lung Solution is used for a final antegrade flush. The trachea and PA cannulae are clamped and disconnected from the system. Once the lungs are removed from the organ chamber, they are stored on ice until transplantation.

EVLP to Optimize Organ Allocation

The longer preservation time permitted with EVLP has the potential to change the landscape of organ allocation by increasing total preservation time. Using standard static cold storage, the entirety of lung preservation is accounted for by cold ischemic time. Currently most centers aim for a cold ischemic time of 8 hours or less when using static cold storage. When using EVLP, the total preservation time is the sum of the first cold ischemic time (CIT1), the duration of EVLP, and the second cold ischemic time (CIT2). A retrospective analysis by Yeung et al. demonstrated that EVLP can be used to safely extend the total preservation time to over 12 hours without negatively impacting hospital and intensive-care unit length of stay, primary graft dysfunction, or short-term survival [12].

Zhang et al. reported similar outcomes increasing cold ischemic time to a mean of 12.0 ± 1.4 hours. Over 4 years, their center performed 9 bilateral lung transplants using high-risk donor lungs conditioned with EVLP using the Lung Assist (Organ Assist BV, Groningen, the Netherlands) perfusion circuit and Toronto Protocol. They observed increased cumulative cold ischemic time in the EVLP group (12.0 ± 1.4 h) compared to the non-EVLP group (7.9 ± 2.7 h). However, this increase in cold ischemic time did not appear harmful, as there were no significant differences observed in primary graft dysfunction or pulmonary function between groups. Over the three-year follow-up period, there were no significant differences observed in survival between groups ($P = 0.73$) [13]. By maximizing CIT1 and CIT2 with intermittent EVLP, the total preservation time can be extended with a non-portable EVLP circuit.

While non-portable EVLP can increase total preservation time by maximizing cold ischemic time, portable EVLP can increase total preservation time while minimizing cold ischemic time. In the INSPIRE trial, Warnecke et al. demonstrated significantly reduced cold ischemic time using the OCS™ Lung system by more than 2 hours ($P < 0.0001$) despite longer total cross-clamp time [11]. Animal studies have also demonstrated that extended periods of preservation is feasible on the OCS™ system for up to 24 hours. However, outcomes were dependent on the specific perfusate used, with erythrocyte-enriched STEEN solution resulting in lower peak airway pressures and pulmonary vascular

resistance compared to allografts perfused with acellular STEEN solution or erythrocyte-enriched low-potassium dextran solution [9]. Whether there is superiority with a particular perfusate or EVLP circuit remains to be seen. Ultimately the longer total preservation time permissible with portable and non-portable EVLP circuits can allow lungs to undergo further assessment and reconditioning, or transported for further distances, thereby reducing the geographic limitations of organ allocation.

EVLP to Improve Allograft Function

With EVLP established as noninferior to static cold storage, recent and ongoing studies have started to assess the ability of EVLP to not only recondition marginal allografts but to improve standard criteria allograft function. The INSPIRE trial randomized standard criteria donor lungs to preservation with the OCS™ Lung device (N = 151) or cold static storage (N = 169. The incidence of severe primary graft dysfunction (PDG) of grade 3 within 72 hours of bilateral lung transplantation was significantly lower in the OCS group compared to the cold storage group (17.7% vs. 29.7%, $P = 0.015$). There was no difference in short-term survival. This was the first prospective randomized trial to demonstrate the ability of EVLP to significantly reduce PGD [11].

An EVLP circuit can also be used as a bioreactor to deliver targeted therapies that would otherwise be harmful or ineffective if administered systemically. Such therapies could be used to engineer allografts prior to transplantation. Figueiredo et al. used the OCS™ Lung device to deliver lentiviral vectors containing short-hairpin RNAs to silence MHC expression on the vascular endothelium in porcine lungs. This resulted in decreased expression of classes I and II swine leukocyte antigen by $60.4 \pm 19.2\%$ and $50 \pm 17.03\%$, respectively. This study is an encouraging initial step towards engineering immunogenically silent organs, potentially eliminating rejection and need for immunosuppression [4].

The use of EVLP as a bioreactor lends itself to applications beyond transplantation. Zinne et al. demonstrated that EVLP could be used to deliver very high doses of antibiotics to treat multidrug resistant pneumonia in a porcine model. In their proof-of-concept study, the left lower lobes of 18 Mini-Lewe pigs were infected with *Pseudomonas aeruginosa*. In the EVLP group, the infected left lower lobe was explanted and perfused on the OCS™ Lung device for 2 hours with STEEN solution supplemented with 1000 ml porcine blood, 500 mg methylprednisolone, 1000 mg amoxicillin, and 800 mg colistin. The left lower lobe was then removed from the circuit, flushed with 1 L of Perfadex and re-implanted in the same animal. Over the five-day study period, the infection-related mortality rate was lower in the EVLP group than in the control and conventional treatment groups (16.7% vs. 66.7% vs. 66.7%). The use of EVLP as a bioreactor for rehabilitation has potential applications in numerous disease contexts and is an area of active ongoing research.

Conclusion

EVLP is an emerging, innovative procedure that plays a very important role in donor lung recovery and evaluation. The use of EVLP has resulted in an increase in LTx using reconditioned marginal donor lungs. The outcomes of LTx with these reconditioned donor lungs appear to be equivalent to that of standard criteria donor lungs. The current disparity between lung transplant candidates awaiting a suitable organ and the number of acceptable donor organs procured may be improved with adoption of this approach. Expanding the donor pool and optimizing lung utilization may lead to an increase in the rate of successful LTx and a reduction in the wait list mortality.

Self-study

1. Which of the following protocol utilizes an asanguinous approach to EVLP?

   A. The Lund protocol
   B. The OCS protocol
   C. The Toronto protocol

Answers

1. C. The Toronto EVLP protocol utilizes a non-blood based perfusion solution with closed left atrial drainage.

Compliance with Ethical Requirements

Consent for Publication All authors provide Springer with consent to publish this work.

Conflict of Interest Dr. Mansour declares that he has no conflict of interest.

Ms. Roberts declares that she has no conflict of interest.

Dr. Lee declares that she has no conflict of interest.

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Animal Studies No animal or human studies were carried out by the authors for this article.

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ECMO Support in Lung Transplantation

Madonna Lee, Daniel Mansour and Bryan A. Whitson

Key Points

- ECMO technologies have continued to improve over the past three decades, and can be used in lung transplant patient pre-operatively, intra-operatively, and post-operatively.
- ECMO can be used safely as a bridge to lung transplantation in patients who experience acute pulmonary function decline prior to receiving a suitable donor organ [1].
- ECMO can replace cardiopulmonary bypass during transplantation [2, 3].
- Post lung transplantation, ECMO can be used support early failing allografts by minimizing permanent injury from barotrauma and oxygen toxicity [4].
- After initiation of ECMO, decreased sedation and active rehabilitation can be performed safely and may lead to improved outcomes [4].

Introduction

Use of extracorporeal membrane oxygenation (ECMO) continues to increase in the past decade. Prior to this, mechanical ventilation was the traditional method of supporting patients with end-stage lung disease, but this support has its limitations, especially considering devastating consequences associated with potentially devasting complications including ventilator-acquired pneumonia, or barotrauma. Mechanical ventilation also offers limited mobility and requiring sedation for comfort, while can lead to deconditioning potentially increasing perioperative risk and limiting recovery from surgery. However, with the establishment of high volume ECMO centers, many applications have been demonstrated to be effective in multiple phases of perioperative care including pre-operatively as a bridge to transplantation [1], intraoperative support as a replacement for cardiopulmonary bypass [2, 3], and post-operative support for delayed graft function [4].

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Indications

The decision to place a patient on ECMO is usually comprised of a multidisciplinary team of different types of care providers including intensivists, surgeons, even physical therapists, or psychiatrists [1]. For ECMO as BTT, several considerations include age less than 65 years, ambulatory functional status before deterioration, no other organ dysfunctions, and good potential for rehabilitation [1]. ECMO therapy bears inherent risks including vascular complications and bleeding [3].

Surgical/Technical Considerations

The determination of whether or not the patient needs veno-venous (VV) ECMO support for purely oxygenation or clearance of hypercarbia, or whether the patient also has circulatory collapse needing veno-arterial (VA) ECMO support will be determined by hemodynamic parameters. If VV ECMO is needed, then using a dual-lumen catheter (Avalon Elite, Fig. 1) is preferred for patients since they can be ambulated. These catheters are placed under transesophageal echocardiogram and fluoroscopic-guidance [1].

Intraoperatively, (see Table 1 **for necessary equipment checklist**) if patients are already on VV ECMO and develop hemodynamic instability, then a 15–17 F arterial cannula can be inserted in the common femoral artery. During transplantation ECMO blood flow was targeted at 4 liter/min, gas flow titrated to carbon dioxide levels and fraction of inspired oxygen at 100% [3]. Post-operatively, continuous infusion of unfractionated heparin (15,000 IU/50 mL) was started greater than 24 hours after ECMO implant with a targeted activated clotting time between 160 and 180 seconds [3].

Removal of ECMO cannulas can be performed without open surgery in patients who had placement done percutaneously. Sometimes cutdown and primary repair of the artery is necessary.

ECMO as a Bridge to Lung Transplantation

Most centers are selective in the patients they use ECMO as a bridge to lung transplantation, including only considering use in patients already listed for lung transplant. In selected high-acuity patients with end-stage lung disease, a single-center series demonstrated successful use of ECMO as a bridge to transplant (BTT) with good short-term survival [1]. Out of 93 patients, 12 (13%) received BTT. It was noted that the mean pretransplant ECMO duration was 103.6 hours (range, 16–395 hours), which may be variable depending on geographic availability of donor lungs. Grade 3 primary graft dysfunction was similar in both groups. All patients who received BTT were decannulated immediately after lung transplantation, but were more likely to return to the OR for a second procedure. These patients also experienced longer hospital stays and higher rates of discharge to rehabilitation centers, but hospital discharge was 100%. 1-year survival was 100% in BTT group. Long-term outcomes are currently being studied [1].

By prophylactically using ECMO is patients as an "awake" strategy and being able to continue ECMO therapy post-operatively, there is some thought that this can modify pre-operative risk for certain patients including patients with pulmonary hypertension. By utilizing ECMO support early, it can reduce the need for using ECMO as a "rescue," therapy after lung transplantation [3].

ECMO as Replacement for Cardiopulmonary Bypass

The use of cardiopulmonary bypass (CPB) during lung transplantation expanded the ability to operate on patients with right heart failure, pulmonary hypertension, the need for concomitant cardiac procedures, and patients who cannot tolerate single-lung ventilation. Some advantages of using ECMO as a replacement for CPB include constant motion of the blood without a

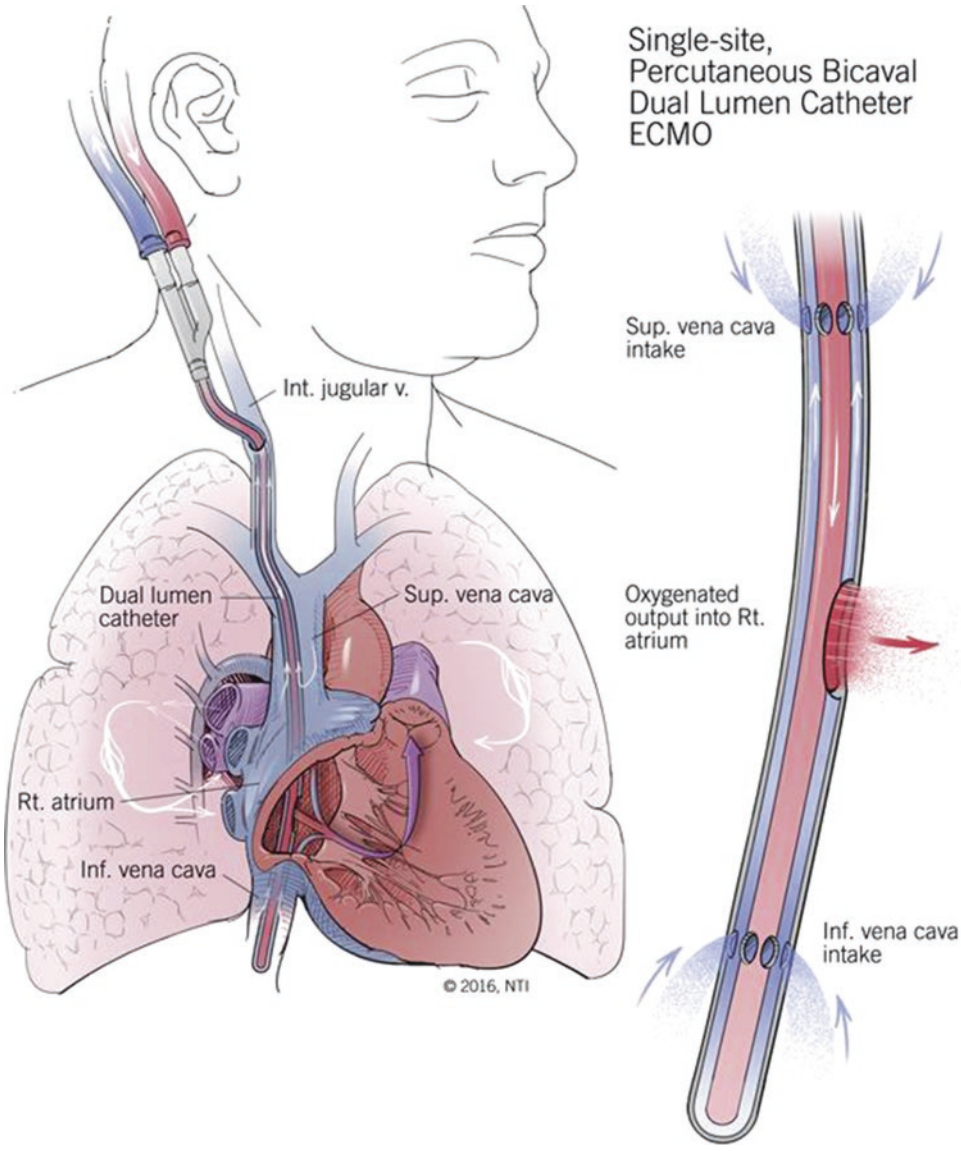

Fig. 1 **a** Schematic of Avalon catheter [1]. **b** Patient with Avalon catheter

venous reservoir, lower activated clotting time targets, and permitting less heparin use [5].

Ius et al., described intraoperative ECMO in lung transplantation as filling the gap between pre-operative and post-operative ECMO. This facilitates integrated perioperative patient management. They demonstrated that over their 5-year single institution experience that patient who required intraoperative ECMO (29%), it was feasible to replace CPB for intraoperative support. The intraoperative use of ECMO did not emerge as a risk factor for in-hospital mortality or mortality after hospital discharge. Survival was similar among patients who underwent transplantation with or without ECMO. Also, they demonstrated that ECMO did not have a negative impact on graft survival at follow-up. Superiority of ECMO over CPB and the comparable survival among patients with or without ECMO depends on pre-operative and peri-operative management strategies and careful patient selection [2, 3].

Table 1 [3] Checklist for catheters/equipment intraoperative

Ius et al. Intraoperative ECMO and Lung Transplantation
Table 1 Checklist for Catheters, Continuously Monitored Parameters, and Devices Required During Lung Transplantation at Our Institution
Catheters
4-lumen central venous catheter[a]
8F introducer[a]
Swan-Ganz pulmonary artery catheter[b]
2 arterial Lines in right radial and left common femoral arteries[a]
3 peripheral venous catheters
Continuously monitored parameters during transplantation
Oxygen saturation
Carbon dioxide levels
Arterial blood pressure from both arterial lines
Central venous pressure
Pulmonary artery pressure
Cardiac output (Vigileo monitor[b])
Devices that must be in operating room before beginning of transplantation
SERVO-i ventilator[c] with nitric oxide supplier
ECMO system

ECMO extracorporeal membrane oxygenation
[a]Arrow International, Reading, PA
[b]Edwards Lifesciences
[c]Maquet Cardiopulmonary AG

In Pittsburgh, Schaheen and colleagues found that ECMO was associated with decreased rate of pulmonary and renal complication, but that early outcomes were not significantly different [6]. If implantation is done without support, then the first lung implanted with exposed to a full cardiac output cycle, which may make it more prone to damage in the setting of already delayed graft function. Thus, by using intraoperative ECMO, the newly transplanted lungs are protected from damage or early overflow [6].

Machuga and colleagues in Toronto matched 33 ECMO cases with 66 CPB cases and found that ECMO was feasible and safe. It was noted that ECMO cases had less mechanical ventilation time, shortened intensive care and hospital stay, as well as less transfusion [7].

There are some advantages of CPB over ECMO technically including full decompression of the heart to perform technically challenging anastomosis, and opening of the pulmonary artery. Also, in certain cases such as infectious etiologies in cystic fibrosis, bronchiectasis, or cavitary lung lesions, certain surgeons may prefer to remove both lungs prior to implantation which is not possible with ECMO [5]. Since CPB can offer more safety and versatility, when massive blood loss is anticipated or a concomitant open procedure is required, CPB should be instituted intraoperatively [6, 8]. There is demonstrated overall survival in patients who had intraoperative ECMO used versus prolonged postoperatively (Chart 1, [9]).

In a single series looking at patients who were either electively on-pump, versus off-pump, versus converting to unplanned on-pump, it appears that these patients may have improved outcomes with an off-pump strategy. However, a considerable proportion of high-risk patients require intraoperative conversion from off-pump to CPB (almost one-third), and this seemed to be associated with suboptimal outcomes including prolonged ventilation, longer ICU admission, and increased need for ECMO post-operatively. There were no statistically significant differences in postoperative outcomes or survival in unplanned conversion groups and a propensity-matched elective on-pump groups [10].

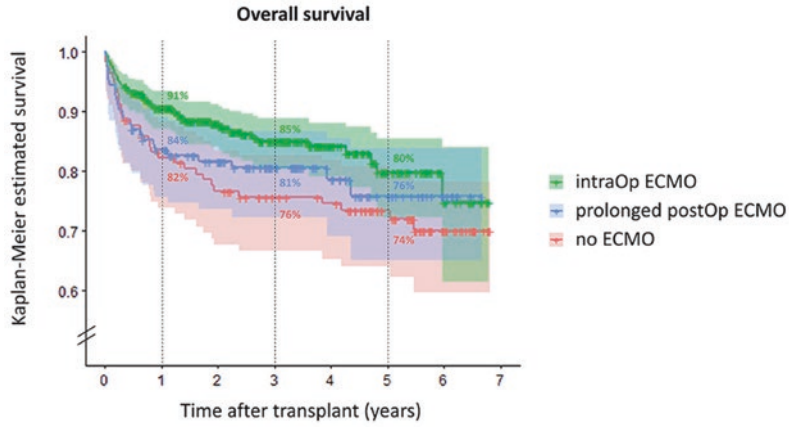

Chart 1 Patients with intraoperative ECMO showed superior survival comparatively [9]

ECMO and Post-lung Transplantation

After some demonstration of ECMO use as safe, and possible more efficacious intraoperatively, in Austria, Hoetzenecker demonstrated that ECMO was associated with improved overall survival compared to patients who did not have ECMO [9]. This has led to a concept in lung transplantation of "prophylactic" postoperative use to try and improve postoperative outcomes (see Fig. 2) [9]. Schaheen and colleagues believe that by utilizing an open chest approach and also ECMO support, some patients including those with pulmonary hypertension and graft dysfunction may have improved outcomes using ECMO post-operatively as compared to not utilizing ECMO support [6]. In fact, there are some centers which use ECMO preemptively.

After implantation, ECMO has been employed as a management strategy to support early failing allografts in lung transplantation. Initiation of ECMO has been advocated early in the postoperative course (<48 h) when ventilatory requirements reach a peak inspiratory

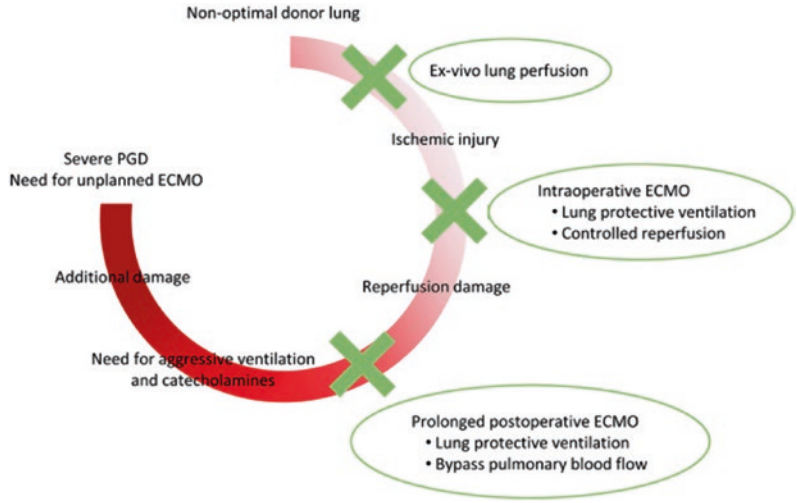

Fig. 2 Vicious cycle of reperfusion injury [9]

pressure of 35 cm H_2O or FiO_2 surpasses 60% in order to reduce oxidative stress and barotrauma from aggressive mechanical ventilation. Both veno-venous and dual-stage cannulation enable patient mobilization. Key management strategies while on ECMO include minimizing sedation, pressure-controlled ventilator support minimizing FiO_2, and maintaining a hypovolemic state as tolerated [4]. Single-center series have documented successful ECMO wean in as high as 96% of patients with 30-day survival of 82% and a 1-year survival of 64% [4].

Conclusion

With establishment of a multidisciplinary ECMO team, hospitals can begin to utilize ECMO in multiple phases of care for patients undergoing lung transplantation. Technically, ECMO cannulas can be placed peripherally with a percutaneous approach, under fluoroscopic and echocardiographic guidance. ECMO is a safe modality to bridge patients to transplantation in patients with end-stage lung disease who experience rapid pulmonary function deterioration [1].

ECMO can serve as a replacement for cardiopulmonary bypass to provide intraoperative support during lung transplantation procedures [2, 3]. ECMO can provide favorable operating conditions by decreasing transfusion requirements, and can be extended to provide support in the post-operative period for primary graft dysfunction [8].

Advances in technology continue to increase the effectiveness of ECMO in early support of failing pulmonary allografts [4]. After initiation of ECMO, decreased sedation and active rehabilitation can be performed safely and may lead to improved outcomes [4]. There is still considerable variability in practice for use of ECMO in lung transplantation [6]. The optimal management strategy for which patients may benefit the most from ECMO support for lung transplantation is still unclear.

Self-study

1. Which of the following statements is true?
   (a) ECMO is safe for use in patients with end-stage lung disease who experience rapid pulmonary function deterioration as a bridge to transplantation
   (b) Decision to place patients on ECMO is usually determined by a multidisciplinary team
   (c) ECMO can serve as a replacement for cardiopulmonary bypass intraoperatively
   (d) Some advantages of using ECMO in lung transplantation include early mobility, avoidance of barotrauma, and decrease sedation
   (e) All of the above
2. Dual-lumen veno-venous (VV) ECMO cannulas inserted in the internal jugular vein should be placed under which type of image-guidance?
   (a) Fluoroscopy
   (b) Ultrasound
   (c) Transthoracic echocardiogram
   (d) Transesophageal echocardiogram
   (e) A + D

Answers

1. E. CORRECT
2. E. Both fluoroscopy and transesophageal echocardiogram are necessary to ensure the dual-lumen is placed in the proper location and that the outflow from the cannula is directed into the right atrium at the junction of the superior vena cava (SVC) [1]

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Extracorporeal Lung Assist Devices

Murughan Kavita and Kollengode R. Ramanathan

Key Points

- The use of extracorporeal devices for respiratory failure has increased in the recent past.
- Different modalities of extracorporeal life support exist, characterized by different vascular approaches, variable designs, non-identical pump dynamics, and different clinical goals.
- ECMO and ECCOR have been successfully used for the management of acute and chronic respiratory failure even in the surgical setting.
- Randomised Controlled Trials for ECMO in acute respiratory failure have shown favourable outcomes; the indications and management of patients are getting streamlined as more evidence accumulates
- Newer pump technologies and better understanding of patient management might enable better outcomes in patients needing extracorporeal lung assist devices.

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Introduction

Acute and chronic respiratory failure remains a common indication for admission to the hospital, especially to the intensive care unit. It is speculated that respiratory failure will be the third most common cause for death by 2025 [1]. The standard treatment for treating respiratory failure is oxygen therapy among which mechanical ventilator support plays a major role. However conventional mechanical ventilatory support on compromised lungs has got deleterious effects on the pulmonary system leading to mortality [2]. John Gibbon, who saw a patient die of pulmonary embolism post cholecystectomy, introduced the concept of extracorporeal cardiopulmonary support. He contemplated that using a temporary cardiopulmonary support system could have changed the outcome, during the embolectomy. This led to the development of an extracorporeal circuit with an artificial oxygenator connected by tubings and the first successful open heart procedure was performed on an 18 year old female with atrial septal defect [3]. Over the last few decades extracorporeal life support has become an invaluable rescue therapy for patients with refractory respiratory or cardiac failure. Recent improvements in extracorporeal

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technology, such as smaller devices, heparinised circuits, and robust percutaneous cannulation techniques, have enabled widespread use of extracorporeal support in different clinical situations [4]. This chapter highlights the evidence for use of extracorporeal membrane oxygenation (ECMO), extracorporeal carbon dioxide removal (ECCOR) and other newer lung assist devices that is currently used in patients with respiratory failure as well as in thoracic surgical patients.

Evolution of ECLS (Fig. 1)

- In 1953 John Gibbon designed the first heart lung machine, which leads to the evolution of modern cardiopulmonary bypass [3].
- At the Boston Children's Hospital, a surgical resident Dr. Robert Bartlett developed a membrane lung to support children post-cardiac surgery till their cardiac function recovered [5].
- In 1971, J. Donald Hill and his colleagues treated successfully a young man who developed ARDS following trauma on ECMO [6].
- In 1975, Robert Bartlett, a thoracic surgeon treated a newborn Esperanza with meconium aspiration syndrome on ECMO [7] .
- Kolobow and Gattinoni in 1978 introduced a modification in gas exchange known as extracorporeal carbon dioxide removal [8].
- Zapol and colleagues in 1979 published the first RCT on ECMO with a conclusion that there was no survival benefit to ECMO [9].
- Extracorporeal Life Support Organization (ESLO) was established in 1989 in Michigan, a community for researchers and practioners to promote data collection from the ECMO centers and to standardize the procedures and protocols [10].
- CESAR trial—a multicenter study in 2008 where conventional ventilatory support versus extracorporeal membrane oxygenation for severe respiratory failure was studied. The study showed better survival rate and lesser disability at six months in ECMO group [11].
- EOLIA trial—ECMO to rescue lung injury in severe Acute Respiratory Distress Syndrome (ARDS) trial evaluated randomly 249 patients with severe ARDS and compared early (within first seven days of mechanical ventilation) versus protective lung ventilation or late ECMO therapy. ECMO resulted in lesser treatment failure and lesser morbidity [12].

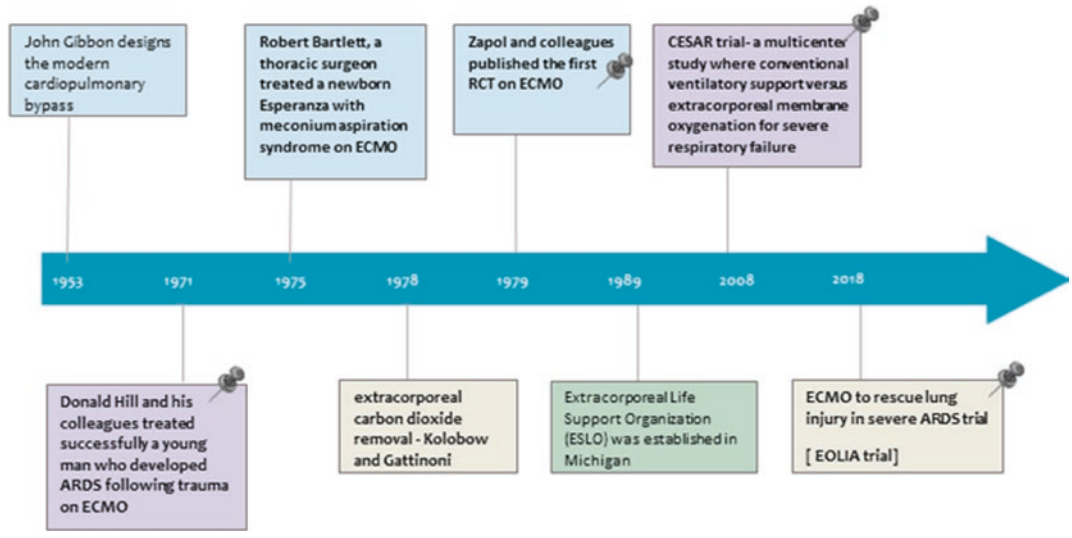

Fig. 1 Timeline showing developments in extracorporeal life support

ECMO as a Lung Assist Device

General Principles

Extracorporeal Membrane Oxygenation is a form of extra-corporeal life support where venous blood from the patient is carried to a gas exchange device (oxygenator) by external cannulas and tubings. Blood gets oxygenated, while carbon dioxide is removed and is returned to the patient's venous or arterial circulation. Circuit flow is achieved using a centrifugal pump. The ECMO circuit consists of a large bore drainage cannula (inserted into a large vein), a centrifugal pump (capable of providing circulatory support), an oxygenator (facilitates exchange of oxygen and carbon dioxide), a heater unit (to maintain blood temperature at an acceptable level) and a large bore return cannula (either inserted into a large vein or artery). During ECMO, venous blood is diverted from the patient and pumped through the oxygenator. The oxygenated blood is then returned to the patient.

Two main forms of ECMO are currently practiced:

(1) Venovenous (VV) ECMO is used to provide gas exchange support for patients with severe respiratory failure refractory to conventional ventilatory support in the context of adequate heart function. Cannulas in large central veins help drain venous blood from the patient which is then returned to the right heart after it has passed through the oxygenator.
(2) Venoarterial (VA) ECMO is used to provide both circulatory and gas exchange support for patients with severe cardiac failure refractory to inotropes, intra-aortic balloon pump (IABP) counter pulsation and ventilation. Venous blood from the patient is accessed from the large central veins and returned to the arterial system in the aorta (femoral, carotid, or axillary artery, or the ascending aorta) after it has passed through the oxygenator.

In the case of VV ECMO the oxygenated blood is returned to the venous circulation, providing gas exchange support only (Fig. 2). In VA ECMO, the oxygenated blood is returned to the arterial circulation (Fig. 3). Therefore, in addition to gas exchange support, the blood pump flows contribute to systemic oxygen delivery and provide circulatory support.

ECMO Circuitry

ECMO circuit consists of a mechanical pump, an oxygenator, a heat exchanger all connected with circuit tubing between the cannulas [13]. The desaturated blood from the patient is drawn

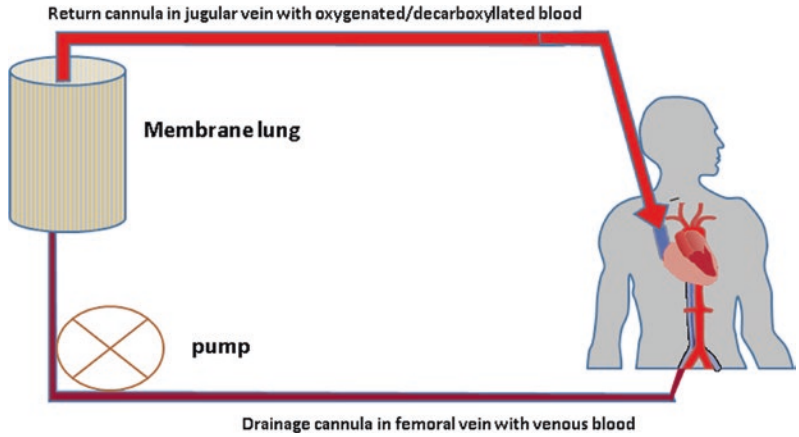

Fig. 2 VV ECMO configuration with deoxygenated blood being drawn from femoral vein and oxygenated blood being retuned back to jugular vein

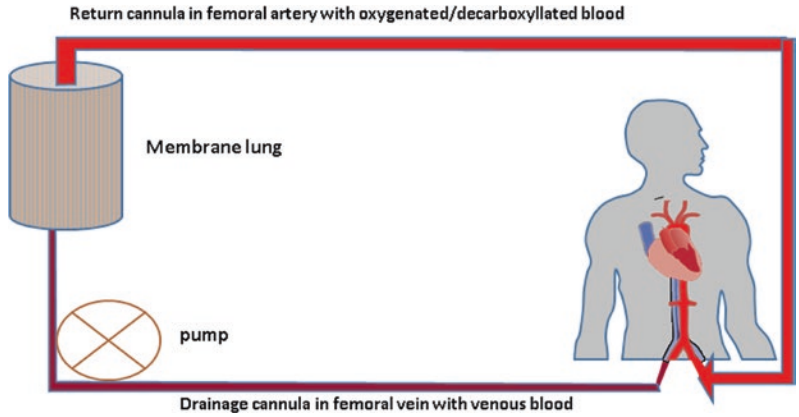

Fig. 3 VA ECMO configuration with deoxygenated blood being drawn from femoral vein and oxygenated blood being retuned back to femoral artery

out from a large vein through a drainage cannula using a centrifugal pump. This blood passes through an oxygenator which helps in gas exchange. The oxygenated blood is then sent back to the patient through the return cannula.

Parts of the Circuit

Cannulas are manufactured from biocompatible polymers like polyurethane; modern cannulas are coated with heparin, which reduces platelet activation and the inflammatory sequelae [14].

Venous cannula—the diameters of venous cannula are between 15–29 Fr and are longer (55 cm) as these cannulas have to reach the right atrium from the point of insertion.

Arterial cannula—the diameter of arterial cannula is between 15–23 Fr and is smaller than venous cannula. The distal tip is perforated. To prevent ischemia distal to the cannula insertion, a 6Fr catheter is introduced for distal perfusion connected to the outflow cannula through a Leur connector.

Tubing: the tubing is made of polyvinyl chloride (PVC) [15]

Pumps: A mechanical blood pump helps the operator to control the flow through the circuit to the patient. The two types of pumps are roller pumps and centrifugal pumps [16]

Oxygenator: The oxygenator aids in gas exchange. The oxygenator used in ECLS circuit is made up of poly-methyl pentene (PMP). These are made up of hollow fibres that separate the blood and gas phase. Oxygen is delivered through the hollow fibres and blood flows around these fibres where oxygen uptake and carbon dioxide removal takes place.

Oxygenation: hemoglobin carries oxygen in the blood and the oxygen transport produces a sigmoid shaped curve

$$\text{Oxygen delivery} = \text{cardiac output x oxygen content}$$

$$\text{Oxygen content} = (\text{Hb} \times \text{SaO}_2 \times 1.34) + (0.003 \times \text{PaO}_2).$$

(Hb-hemoglobin concentration in grams pre 100 ml blood, SaO_2-percentage saturation of Hb with oxygen, 1.34 the amount of oxygen bound per gram of Hb, PaO_2-partial pressure of oxygen, 0.03 the amount of O_2 dissolved in plasma.)

Factors that determine oxygenation in an extracorporeal circuit are

1. Blood flow rate
2. Diffusion of oxygen through the hollow fibers
3. Membrane surface area
4. Oxygen saturation of preoxygenator blood
5. Hemoglobin concentration.

Carbon dioxide (CO_2) removal: The CO_2 produced by metabolism in the mitochondria exists as dissolved form (5%), bicarbonate ion (90%) and as carbamino compound (5%) CO_2 diffuses more rapidly than oxygen through the artificial membranes, as it is highly soluble. Factors that determine CO_2 removal on ECMO:

1. Sweep gas flow
2. Blood flow
3. Membrane surface area [17].

The standard settings and goals of patient management on ECMO are given in Table 1.

Use of ECMO as a lung assist device

[A] ECMO in respiratory failure

- Pulmonary infections
- Lung trauma
- Airway surgeries and lung resections
- Bronchopleural fistula

[B] ECMO and mediastinal masses
[C] ECMO and pulmonary embolism
[D] ECMO and lung transplantation.

Table 1 ECMO goals and settings

Parameters	Settings
Circuit flow [LPM]	50–100 ml/kg/min
Sweep gas flow [LPM]	50–75 ml/kg/min
Fractional inspired oxygen (FdO2)	100%
$PaCO_2$	35–45 mmHg
pH	7.35–7.45
Inlet pressure	>100 mmHg
Oxygen saturation (drainage cannula)	>65%
Oxygen saturation (return cannula)	100%
Peripheral sPO2	VA >90%, VV >85%
Mixed venous oxygen saturation	>65%
Mean arterial pressure	60–65 mmHg
Hemoglobin	8–11 g/dL
Platelet count	>50,000 mm^3

[A] ECMO in respiratory failure

Over the years the treatment of acute respiratory failure has progressed from simple oxygen therapy through conventional mechanical ventilator support to lung protective ventilation and prone ventilation. ECMO remains a salvage therapy in the management of refractory hypoxemic or hypercapneic respiratory failure. ARDS secondary to pneumonia remains the most common cause of respiratory failure needing ECMO therapy. ECMO has also been used as a salvage therapy in other causes of respiratory failure including asthma, aspiration pneumonitis and sepsis [18].

- **Pulmonary infections**: Even though ECMO was being used for respiratory infections ever since it was pioneered by Bartlett et al. in 1972, the CESAR trial underlined its importance in the modern era. Following the CESAR trial, ECMO was used for severe influenza-induced acute respiratory distress syndrome (ARDS) in Australia and New Zealand during the influenza A (H1N1) pandemic, with high survival rates (79%) [19]. An analysis of the ELSO registry for adults with community acquired pneumonia who needed ECMO between 2002–12 revealed that the overall survival in this group of patients is 66%. [20] Veno venous ECMO was the most common mode initiated in 92% of the patients with Influenza being the most common organism implicated. Patients with respiratory infections on ECMO had higher mortality with increasing age, prolonged duration of MV (>6 d), and low arterial pressure. Patients with fungal infections needing ECMO had a higher mortality while venoarterial mode was associated with significantly higher mortality than venovenous mode. The duration of ECMO run was an independent predictor of mortality; patients with more than three complications on ECMO had a higher risk of mortality on ECMO [20].

The use of ECMO to maintain adequate gas exchange in patients with severe respiratory

failure needing general thoracic surgery to drain infections has been sparsely reported in literature. Till date there are only few case reports that has reported the use of ECMO to facilitate drainage of empyema and lung abscess via thoracotomy and single lung ventilation [21, 22] Brenner et al. reported a successful case of thoracotomy and decortication with VV-ECMO support in a 45-year-old male who had ventilator-associated pneumonia and the development of a left-sided empyema after a motorbike accident [21, 23].Similarly Souilamas et al. [23] reported a patient with refractory pulmonary aspergilloma presenting with recurrent haemoptysis who needed VV-ECMO using an Avalon cannula to support single lung ventilation for segmentectomy. Even though the patient had poor preoperative lung function was borderline, ECMO support was successfully weaned 12 hours after surgery.

- **Lung trauma**: The first successful use of ECMO was reported in a polytrauma patient in 1972 [6]. Trauma is associated with systemic inflammation and complications such as pneumonia, sepsis, and subsequent respiratory failure which needs supportive care, with lung-protective ventilation in ICU [24]. Patients who develop adult respiratory distress syndrome (ARDS), have a mortality rate between 45–60% despite appropriate and aggressive supportive care [25]. In a systematic review of literature that looked at the safety and efficacy of VV-ECMO in posttraumatic ARDS, the authors advocated use of VV-ECMO as a salvage therapy for severe respiratory failure arising from ARDS in trauma patients [26]. They suggested the use of a robust anticoagulation regime that included no initial anticoagulation in patients with high bleeding risk while the use of heparin aiming an ACT < 150 seconds was found to be optimal for patients with a moderate risk of bleeding. Polytrauma, myocardial contusion with refractory hypotension is few indications of extracorporeal support in trauma. Guirand et al. conducted a multicenter retrospective cohort study where VV-ECMO in trauma related ARDS improved the 60-day survival rate. [27] The case series of 26 trauma patients who required VV-ECMO for ARDS following severe traumatic injuries showed an unadjusted ECMO survival rate of 57.7%. Further propensity score matching for age and PaO2/FiO2 ratio with 17 ECMO and 17 conventional patients showed ECMO patients survived better: (Kaplan Meier survival 64.7% vs. 23.5%, $p = 0.01$). A retrospective observational analysis of the Regensburg ECMO Registry database for trauma patients with acute respiratory failure requiring extracorporeal lung support showed good survival rates with VV-ECMO (81%) and pumpless extracorporeal lung assist (77%) during a 10-year interval [28]. Larsson and colleagues surveyed the role of VA ECMO in trauma patients and concluded that it can control pulmonary bleeding during surgery [29]. Traumatic brain injury [TBI] has been considered a relative contraindication to ECMO; however, several reports have been published on ECMO in patients with TBI [30–32]. It is difficult to make definitive recommendations with currently available evidence; however the risks and benefits of ECMO should be evaluated on a case-by-case basis in patients with TBI.
- **Bronchopleural fistula**: Bronchopleural fistulas [BPF] occur as major complications following traumatic lung injury or following lung resection surgeries. The prognosis is made worse by the fact that mortality rates remain as high as 67% in patients with BPF requiring mechanical ventilation, and 94% in case of a large air leak (>5 mL/kg [33]. Daoud et al. reported a case series of five patients with postsurgical BPF with refractory ARDS where VA ECMO permitted lung-protective ventilation [34]. These patients were refractorily hypoxemic and had failed the conventional modes of ventilatory management of ARDS; they were able to successfully wean 3 of the 5 patients and discharge them from the hospital following healing of BPF. There are a few case reports that describe the successful use of extracorporeal lung assist

devices in the management of BPF associated with ARDS. VV-ECMO was successfully used to treat a patient with anastomotic fistula after lung transplantation [35] while a pumpless extracorporeal lung assist device was used successfully in 4 patients with postsurgical BPF [36]. VV-ECMO is indicated in massive air leak to maintain oxygenation. Patients can undergo VATS or open surgery while on ECMO [36].

The contrasting and contradicting therapeutic requirements for the management of BPF in the context of ARDS throws a clinical challenge in maintaining adequate gas exchange with the need to promote BPF healing. The use of VA ECMO to treat this condition should be viewed as salvage in hemodynamic unstable patients in whom traditional lung protective ventilation has failed. VV-ECMO should be used in patients without hemodynamic compromise.

[B] ECMO for airway and lung resection surgeries

Use of extracorporeal life support to facilitate extended airway surgery or endoscopic airway manipulation in critical obstructions is gaining popularity among the thoracic surgeons [37]. Major airway surgeries require optimal exposure and maintenance of adequate gas exchange. Conventional jet ventilation with periodic apneoa, is usually sufficient to provide excellent surgical field. However in instances where airway control is difficult or near impossible or when there is an anticipated imminent danger of losing an airway ECMO remains a safe option to support the patient's respiratory functions during the surgery. Even though Woods et al. [38] described the first airway surgery using cardiopulmonary bypass in 1961, the first use of ECMO in airway surgery happened 31 years later when Walker et al. in 1992, reported a case of a 2.5 kg infant needing segmental resection and end-to-end anastomosis for congenital tracheal stenosis [39]. Peripheral ECMO support was initiated and it enabled surgery without sternotomy, requiring less heparin, and facilitated the anticipated postoperative airway healing on ECMO. Connolly et al. published first case series using ECMO for intraoperative ventilatory support in pediatric patients needing airway surgeries [40]. Ever since, ECMO has proven to be a powerful tool in extended airway surgeries in large thoracic centres. ECMO support has been extensively published for complex endoscopic airway intervention. Hong et al. reported the largest series of 18 ECLS patients with different tracheal malignancies during endoscopic airway intervention [41]. They showed excellent results with 17 out of 18 patients being successfully weaned from ECMO. They observed that in spite of anticoagulation and extensive endoscopic tumor debulking; only 2 patients had significant bleeding proving that ECMO could be a safe option in these circumstances. Pre emptive ECMO should be considered in significant intrathoracic airway stenosis, patients needing complex lower airway/carinal reconstruction and in situations where airway occlusion is expected temporarily [37].

There is a dearth of literature on the use of ECMO for during conventional thoracic surgery even though there are reports on improved survival in patients with post-pneumonectomy ARDS [42]. Intraoperative ECMO can ensure good hemodynamics with good surgical exposure or help one-lung ventilation in select thoracic surgical scenarios. Rinieri et al. reported a national review involving 34 thoracic centres in France on the use of ECMO as respiratory support during 2009–2012 [43]. Out of the 36 patients from 17 centres, 28 patients in Group 1 needed ECMO for full respiratory support during procedures of the upper airway or to permit single lung ventilation intraoperatively. 5 patients in group 2 needed partial VV ECMO support for lung resections, fistulas and trauma. 3 patients in-group 3 had prolonged ECMO as part of their ARDS and were operated for lobectomy. Overall 30-day mortality was 17% with mortality in Groups 1, 2 and 3 being 7, 40 and 67%, respectively ($P<0.05$). Patients with preexisting ARDS and prolonged ECMO did poorly compared to the rest of the cohort. ECMO was weaned intraoperatively or within 24 h in 75% of patients in group 1 compared to

over several days in Group 2 [43]. Intraoperative emergencies such as cardiac instability from major cardiac retraction or severe pulmonary hypertension should necessitate peripheral or central VA ECMO depending on the accessibility based on patient position. Upper airway surgeries like tracheo-carinal resection, with no hemodynamic instability should obviate VV-ECMO for intraoperative respiratory support. As thoracic surgery evolves further, centers with extensive experience and patient volumes have started showing good outcomes by using ECMO as total respiratory or cardiorespiratory support in select group of patients where conventional ventilation techniques are not feasible [44].

[C] ECMO and mediastinal masses

Tumors such as malignant lymphoma and non-small-cell lung cancer can cause superior vena cava (SVC) syndrome and obstruction of the major airways. [45] Anterior mediastinal masses frequently require biopsy for diagnosis and further surgical resection, chemotherapy, and radiation as part of their therapy. Large anterior mediastinal masses can compress airway and vascular structures to cause acute cardiopulmonary decompensation at the time of induction of anesthesia. The ensuing hemodynamic compromise is complicated by the fact that general anesthetics and neuromuscular blockers worsen the extrinsic airway compression by relaxing the skeletal muscles. Furthermore, structures including the heart and the pulmonary artery may be compressed resulting in increased right ventricular afterload and worsening heart failure The use of ECMO in this scenario permits maintenance of perfusion of oxygenated blood despite impaired ventilation and avoids the anesthetic risks [46, 47]. In patients with narrowing of intrathoracic airways by a significant mediastinal mass, ECMO initiation should be planned under local anesthesia and light sedation. Biopsy or planned resection of such tumors can then proceed once ECMO is initiated [48].

[D] ECMO and Pulmonary embolism

The spectrum of clinical presentation and clinical outcomes in patients with pulmonary embolism is highly variable. While patients presenting with mild symptoms have a mortality less than 1% patients with massive PE with concomitant shock have mortality higher than 30%. There are currently no international guidelines that include ECMO as part of the standard algorithm for treatment of PE; however there are patients with massive pulmonary embolism leading to cardiorespiratory failure who have been reported to be managed on ECMO. The Task Force on the diagnosis and management of pulmonary embolism of the European Society of Cardiology mentions experimental evidence for extracorporeal life support for patients with massive PE supported by evidence from case reports and series [49]. Patients can be prepared for thromboprophylaxis and a vena caval filter or for pulmonary embolectomy with ongoing ECMO support [50].

Physiologically ECMO remains the most reliable and the quickest salvage therapy to reduce pulmonary vascular resistance and improve hemodynamics with oxygenation in this scenario. VA ECMO enables diversion of blood from right heart, thereby reduces the right ventricular overload and increases the cardiac output in patients hemodynamically compromised from massive PE. Preoperative cardiac arrest requiring CPR remains an independent risk factor for mortality in up to 59% of patients with massive PE; hence experienced centres embark on aggressive treatment protocols that include extracorporeal life support for management of massive PE. Clinical outcomes from such units show a drastic reduction in mortality to less than 10% [51–53]. In a single centre series, Pasrija et al. showed that a strict protocolised management of massive PE patients with timely ECMO could have survival rates up to 95%. [53] Patients with diagnosed massive PE underwent VA ECMO if their systolic blood pressure was less than 90 minutes for at least fifteen minutes with or without inotropes or if they had severe bradycardia despite inotropic support. Patients were then systemically anticoagulated for five days and their VA ECMO continued till their neurological status was ascertained if it was unclear initially or till end organ

function improved. Any evidence of persistent RV dysfunction despite anticoagulation on repeat echocardiography prompted early surgical embolectomy on ECMO [53]. Recently published data from the largest multicenter series of 52 patients with high risk PE needing VA ECMO showed that high-risk PE patients on ECMO have a more severe presentation and worse prognosis. VA ECMO in patients who failed thrombolysis and in those with absent reperfusion have an unfavorable prognosis compared with ECMO plus surgical embolectomy. [Mortality—No ECMO versus ECMO with thrombolysis versus ECMO with surgical embolectomy: 43% vs. 61.5% vs. 29%] [54].

ECMO outcomes in massive PE patients are very poor if used as a stand-alone treatment strategy, but outcomes are better when used to complement surgical embolectomy.

[D] **ECMO and lung transplantation**

Extracorporeal support as a bridge to lung transplant have promising survival rate comparable to patients treated on mechanical ventilator support prior to lung transplant Primary graft dysfunction occurs in 15–30% of patients with lung transplant and is a major cause of death following lung transplantation. Postoperative extracorporeal support in lung transplant patients can be beneficial by reducing barotrauma and toxicity to the lung.

The use of ECMO as a bridge to as well as after lung transplantation has been discussed separately in another chapter.

ECCOR as a Lung Assist Device

ECCOR predominantly removes carbon dioxide (CO_2) and unlike ECMO, it does not contribute to significant oxygenation or hemodynamic stability. ECCOR circuit is a miniaturized version of the ECMO circuit and essentially consists of a drainage cannula, a centrifugal pump, an artificial gas exchange system and a return cannula. Blood is drained from a large central vein through the drainage cannula and is pumped through the membrane 'lung', which removes CO_2 by diffusion. A gas flow with little or no CO_2 on the other side of the membrane creates a gradient for diffusion that favours CO_2 removal. Given the differences in CO_2 and oxygen (O_2) kinetics, ECCOR allows much lower blood flow rates as compared to ECMO [55].

Gattinoni et al. [56] introduced ECCOR in 1978, in patients with severe ARDS using a membrane lung, and a roller pump, where it was combined with lung protective ventilation resulting in a mortality was 51% [8], the technique has undergone several modifications since then; currently used ECCOR techniques can be classified into (i) arteriovenous devices, AV ECCOR and (ii) venovenous devices, VV ECCOR.

General Principles

AV-ECCOR (Fig. 4)

The pumpless arterio-venous ECMO was introduced in clinical practice in the 1970s to remove CO_2 from blood using the arterial blood pressure in an arterio-venous system with a hollow fibre oxygenator. The cardiac output and the mean arterial pressure determines the driving force for the blood flow. In 2002 the first commercially available AV-ECCOR system was introduced. AV- ECCOR is commercially marketed as the interventional lung assist (iLA) membrane ventilator or the Nova lung. Cannulas are inserted into the femoral artery and vein and an artervenous pressure gradient [>60 mm Hg] enables gas exchange through a low resistance membrane lung. AV ECCOR can be used in hemodynamically stable patients; however limb ischemia secondary to arterial cannulation and bleeding are the major complications in this system [57, 58]. Case reports on the successful use of AVCO2R has been published in patients with severe asthma [59], ARDS [60] and as a bridge to lung trans plantation [61] (Fig. 4).

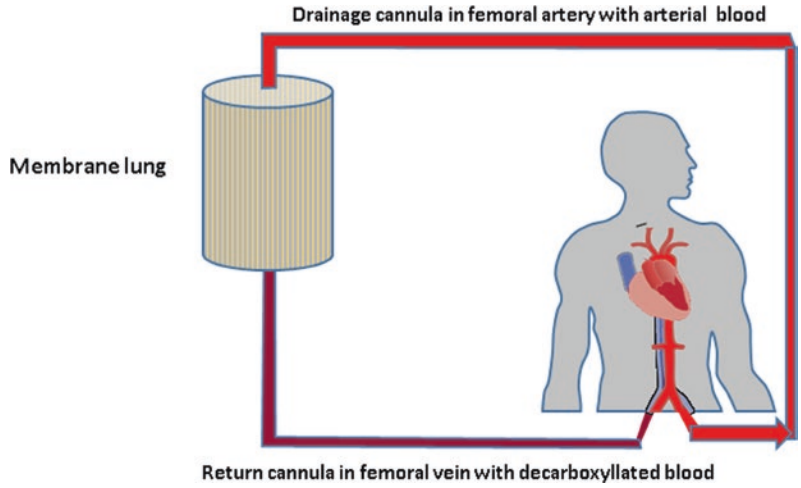

Fig. 4 AV ECCOR configuration with blood being drawn from femoral artery and decarboxylated blood being retuned back to femoral vein

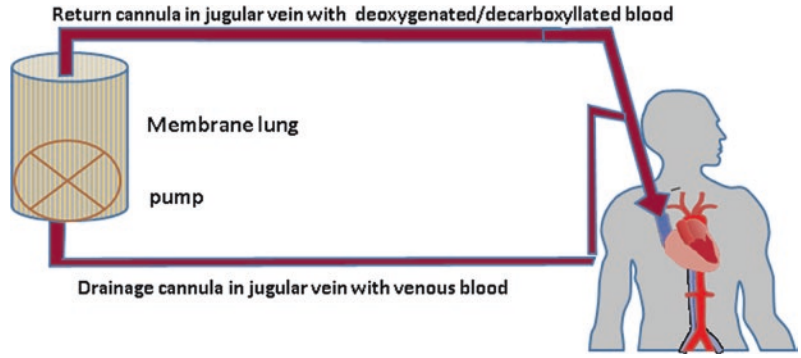

Fig. 5 VV ECCOR configuration with blood being drawn from jugular vein and decarboxyllated blood being retuned back to jugular vein

VV-ECCOR (Fig. 5)

This is one of the earliest forms of extracorporeal support for CO_2 removal. Gattinoni et al. treated patients with severe respiratory failure requiring low frequency positive pressure ventilation with ECCOR [28] with no significant survival benefit. Venovenous carbon dioxide removal (VV ECCOR) requires an external pump to circulate blood across a membrane lung at flow rates >1 Lpm. Modern ECCOR machines incorporate the the pump and membrane lung into a single console (Fig. 5).

Modern VV-ECCOR (Low Flow Technique)

These systems use double lumen venous cannulation, connected to a circuit driven by a pump. The cannula used is smaller in size measuring 14Fr. The system uses a membrane lung for carbon dioxide removal and may use a hemofilter. along with to aid dialysis [62].

Three such systems currently used in clinical practice includes [55]:

- **Decap**: It uses a roller pump, which can achieve a flow rate up to 400 mL/min. The circuit also contains a hemofilter, which controls the lung kidney interaction in multioragan failure. The hemofilter also reduces bubble formation within the membrane lung and aids additional CO_2 removal by recirculating the ultrafiltrate.
- **iLA Active**: The system uses venovenous configuration, which supports the respiratory system for an effective removal of carbon dioxide. The iLA Active mounts the membrane lung and a diagonal flow pump together in one device.
- **Hemolung**: The Hemolung device combines the membrane lung and centrifugal pump into one unit. A rotating impeller draws blood into a rotating core chamber that pushes blood towards a surrounding stationary fiber bundle resulting in active mixing; this enables more efficient CO_2 removal at flows of 400 to 600 ml/min.

Clinical Uses of ECCOR

ECCOR in chronic obstructive pulmonary disease (COPD): Acute exacerbation of COPD generally gets treated with NIV. However NIV fails in 50% of the patients who are subjected to mechanical ventilator support. Mortality in this group of patients ranges between 25–39%. ECCOR can be used to support lung function with no invasive ventilation. In 1990 Pesenti et al. presented the first case of successfully treating a COPD patient with ECCOR. There are numerous case reports presenting the beneficial effects of ECCOR in COPD treatment as an adjunct to mechanical ventilation. [62, 63] Burki et al. used a single venous catheter ECCOR system in patients with acute exacerbation of COPD [63]. The ECCOR system reduced intubation in all patients who failed NIV and was a feasible adjunctive therapy during acute exacerbation of COPD. Ongoing trials using low flow ECCOR will confirm the utility of this device in patients with exacerbations of COPD.

ECCOR in ARDS

Gattinoni in 1970s applied ECCOR for the treatment of ARDS to minimize the complications of mechanical ventilation on the pulmonary system [56]. However early studies on ECCOR in ARDS did not show favorable outcomes. The last decade saw improvisation in extracorporeal support, thereby improving the efficacy of ECCOR in treating ARDS. AV ECCOR and VV ECCOR have been used with limited success in the management of hypercapnia associated with lung protective ventilation for patients with ARDS. ECCOR assisted low tidal volume ventilation was associated with reduction in inflammatory markers in response to ventilator associated lung injury. A comparative study-treating moderate to severe ARDS with conventional ventilatory support and with ECCOR assisted low tidal volume ventilation (3 ml/kg PBW) revealed significant ventilator- free days in the ECCOR group [64, 65].

Other Clinical Uses of ECCOR

ECCOR has been used in elective and emergency thoracic surgeries. Till now there are only few case reports supporting the use of ECCOR in thoracic surgery. ECCOR permits one lung ventilation in patients with poor respiratory function. Wiebe et al. used Nova lung in ten patients needing major thoracic surgery that permitted one lung ventilation or prolonged apneic intervals intraoperatively. The authors used low dose noradrenaline to maintain flow across the Nova lung [66]. There are case reports that report the successful use of ECCOR in the treatment of bronchopleural fistulas, lung trauma and as bridge to lung transplantation [32, 36, 58].

Other Lung Assist Devices

Intravascular Gas exchange catheters

IVOX: The intravenocaval oxygenator can also function as a device for CO_2 removal; it consists

of hollow fiber membrane lungs that is packaged into a catheter [< 15 mm diameter] and placed in the vena cava [55]. These intracorporeal catheters are exposed to 2 to 3 L/ minute of blood flow and therefore gas exchange is not flow limited. IVOX has been used in smaller observational studies and case series; the results have been equivocal. While it facilitated ultra-low volume ventilation in some studies [67], it did not have any clinical impact in others [68, 69]. Overall it was found that gas exchange was too limited and procedure related complication rates from bleeding and thrombosis were high [69].

Hattler catheter: Hattler catheter closely resembles an intra-aortic balloon pump; however it has a rigid fiber mat around a central balloon that favours active mixing when rapid pulsation of the balloon causes blood flow over the membrane fibers [70]. The catheter has been used in animal studies with good results compared to the IVOX catheter [71].

Respiratory dialysis

This concept uses dialysis to remove CO_2 in the form of bicarbonate. CO_2 is transported as bicarbonate in blood, which can move freely across dialysis membranes [55]. Conventional hemodialysis that uses bicarbonate-containing dialysates can be modified to remove enough CO_2 to replace pulmonary ventilation in dog models [72]. Experimental research involving use of sodium hydroxide and tris hydroxymethyl amino methane [THAM] as replacement fluids in dialysis has been tried in animal models for CO_2 removal. Respiratory dialysis is a promising concept that may enable extracorporeal lung support using dialysis machines if the problems relating to electrolyte and acid-base disturbances can be rectified [55].

Complications of Extracorporeal support

The use of extracorporeal support for lung assistance is not without complications. A summary of the common complications is listed below:

- Pump related complications

Hemolysis: Excessive circuit chattering, extremes in negative pressure generated by the pump, partial circuit thrombosis can cause hemolysis and raised plasma hemoglobin in patients on extracorporeal life support. It is essential to check the level of plasma hemoglobin while on extracorporeal support and maintain it less than 10 mg/dl. Elevation more than 50 mg/dl is significant and the cause should be investigated. [38]

Air embolism: Inadvertant air entry through a break in circuit between the patient and the pump is possible. Sensors are placed at the outlet of the oxygenator, which detects air bubble in the system [39].

Power failure: An alarm is generated whenever there is low or reverse flow or if the power fails. In the event of pump failure, a battery, which lasts for an hour, supports the pump; also the care provider should be able to manually crank the pump to prevent a catastrophic event [40].

- Bleeding: Bleeding can occur at the cannula site, or previous invasive procedure site, internal bleeding. The bleeding process is aggravated by systemic heparinisation, thrombocytopenia and coagulation dysfunction [41].
- Vascular complications: The most common complication is limb ischemia on peripheral VA ECMO. A distal perfusion cannula is inserted to avoid hypo perfusion. Patients may need fasciotomy or amputation for severe limb ischemia unresponsive to distal catheter insertion.
- Cardiopulmonary: arrhythmias, hypertension, pericardial effusion, cardiac tamponade.
- Pulmonary: Pulmonary hemorrhage and pneumothorax are not uncommon while on ECMO.
- Neurological complications: 10–15% on ECMO develop intracranial hemorrhage or infarct [43]. Hemorrhagic infarcts need cessation of anticoagulation.
- Renal failure: Renal failure on extracorporeal life support is usually multifactorial. Renal replacement therapy is initiated if indicated.
- Hematological: Anemia, heparin induced thrombocytopenia is also common in ECMO

patients. When HIT is diagnosed, heparin infusion is replaced by bivalirudin or argatroban [44].

- Infection: ECMO cannulas are large foreign material in the body and frequent manipulation of circuit predisposes to infection. Close vigilance on infection control is mandatory.
- Metabolic related: metabolic acidosis, hypoglycemia, hyperglycemia, and hyperbilrubinemia. Increased volume of distribution leads to alteration in serum concentration of the drugs.

Conclusion

The last decade has witnessed advances in extracorporeal technology; also there are upcoming evidences and guidelines for timing and initiation of extracorporeal life support. While the use of ECMO in respiratory failure is fairly established, extracorporeal carbon dioxide removal shows great promise in select patients with respiratory failure. Advanced thoracic surgical centres have started adopting an ECLS based protocol for management of sick patients with severe respiratory failure, needing elective and emergent surgeries. Future research on newer indications, cannulation techniques and pump miniaturization as well as management would throw more light on better evidence based management of these devices and revolutionize management of respiratory failure.

Self-study

(1) The following completes an ECMO circuit except
   a. Mechanical blood pump
   b. Gas exchange device
   c. Heat exchanger
   d. IABP

(2) CO2 clearance on ECMO is dependant on all except
   a. Sweep gas
   b. Blood flow
   c. Membrane surface area
   d. Circuit tubing

(3) VA ECMO in massive PE does the following except
   a. Enables diversion of blood from right heart
   b. Increases the right ventricular overload
   c. Enables better oxygenation
   d. Increases the cardiac output.

(4) ECCOR predominantly removes
   a. CO_2
   b. Ammonia
   c. Urea
   d. Bilirubin

(5) ECCOR can be used in all these conditions except
   a. Thoracic surgery
   b. Severe respiratory failure
   c. Cardiogenic shock
   d. COPD

Answers

(1)D
(2)D
(3)B
(4)A
(5)C

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Surgery for Chronic Thromboembolism Affecting the Lungs

Pulmonary Endarterectomy

Fouad John Taghavi, Choo Yen Ng, David Jenkins, and Steven Tsui

Abbreviations

BPA	Balloon Pulmonary Angioplasty
CPB	Cardiopulmonary Bypass
CTE	Chronic Thromboembolism
CTED	Chronic Thromboembolic Pulmonary Disease
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
CT-PA	Computed Tomographic Pulmonary Angiography
CXR	Chest Radiograph
DHCA	Deep Hypothermic Circulatory Arrest
ECMO	Extra-corporeal Membrane Oxygenation
FC	World Health Organisation Functional Class
mPAP	Mean Pulmonary Artery Pressure
MRA	Magnetic Resonance Angiography
PCWP	Pulmonary Capillary Wedge Pressure
PE	Pulmonary Embolism
PEA	Pulmonary Endarterectomy
PH	Pulmonary Hypertension
PVR	Pulmonary Vascular Resistance
TTE	Transthoracic Echocardiogram
V/Q scan	Ventilation-Perfusion Scan
6MWD	6 minute Walk Distance

Introduction to Chronic Thromboembolic Pulmonary Hypertension

Acute pulmonary embolism (PE) is very common and affects 200–800 people per million of population per annum. In the vast majority of these cases, it resolves after a period of systemic anticoagulation. However, in approximately 4–5% of these patients, the acute PE become organised with fibrotic transformation resulting in chronic obstruction of the pulmonary artery and persistent pulmonary hypertension. This in turn causes remodelling of the pulmonary microvasculature and disease progression. Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as pre-capillary pulmonary hypertension with mean pulmonary artery pressure (mPAP) >25 mmHg, pulmonary capillary wedge pressure (PCWP) <15 mmHg and pulmonary vascular resistance (PVR) >2 Wood units, with at least one segmental perfusion defect in imaging after 3 months of anticoagulation. CTEPH is group 4 of the pulmonary hypertension classification. Some patients develop post-embolic exercise intolerance in the absence of pulmonary hypertension i.e. mPAP <25 mmHg.

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This condition has been referred to as chronic thromboembolic pulmonary disease (CTED).

The prognosis of pulmonary hypertension is highly variable and depends upon the aetiology and severity. With appropriate therapy, patients with CTEPH, particularly the ones with a surgically operable pattern of disease have the best survival [1].

Incidence

The incidence of CTEPH is unknown, but estimates in the literature range between 0.4% and 8.8% amongst survivors of acute PE. Two prospective series have reported that 3.8% and 4.8% of patients develop CTEPH within a 2-year period following the initial diagnosis of PE [2, 3]. A review of 16 studies totaling 4,047 PE patients suggest an incidence of approximately 3% [4].

Risk Factors

It is unknown why some patients develop CTEPH following an acute PE whilst the majority don't. An underlying hypercoagulable state may be responsible in certain patients. Studies have shown that patients with elevated Factor VIII levels and antiphospholipid antibodies are more prone to developing CTEPH. However, not all abnormalities associated with a hypercoagulable state are linked to CTEPH. Activated protein C resistance occurs with a similar frequency in both the general population and CTEPH patients, and <1% of CTEPH patients have deficiencies of protein C, S or antithrombin. Other associated conditions including previous splenectomy, presence or history of infected ventriculo-atrial shunts, indwelling catheters and pacing leads, and hypothyroidism also pose as risk factors in developing CTEPH post-PE.

Likewise, the pathology of CTEPH is not completely understood. The most widely accepted hypothesis is that the acute thromboembolism transitions to a chronic endothelialised endovascular scar [5]. It is believed that a combination of localized inflammation, ineffective angiogenesis and endothelial dysfunction results in maladaptive vessel wall re-modelling with poor resolution of the thrombus [6, 7]. The organisation of the clot proceeds to re-canalization producing multiple small endoethelialised channels giving a characteristic web pattern. On the other hand, if fibrous organisation of the clot occurs without re-canalization, this leads to a dense cast of fibrous tissue completely obstructing the arterial lumen. Over time, a distal pulmonary vasculopathy develops which is similar to that seen in idiopathic pulmonary hypertension [8]. Pulmonary hypertension due to distal pulmonary vasculopathy is not reversed by surgery and its development is a poor prognostic factor.

Clinical Presentation

There are no specific symptoms in patients with CTEPH. They usually present with progressive dyspnoea and exercise intolerance. This dyspnoea is often out of proportion to any abnormalities found on clinical examination. Some patients delay seeking medical advice and then present late with signs and symptoms of right ventricular dysfunction, such as peripheral oedema, exertional chest pain, pre-syncope or syncope.

Many patients describe a history of an acute venous thromboembolic event, months to years preceding the worsening dyspnoea. However, a documented history of venous thromboembolism is only present in about two thirds of surgical CTEPH patients.

The physical signs of pulmonary hypertension are not specific to the underlying pathophysiology and may be rather subtle early in the course of the disease. However, once there is significant right ventricular hypertrophy or right ventricular failure, signs such as jugular venous distension, prominent A and V waves, fixed splitting of the second heart sound, tricuspid regurgitation murmur with an enlarged pulsatile liver, ascites and peripheral oedema can all be observed. The peripheral oedema may either be due to right heart failure or chronic lower extremity venous insufficiency.

In some patients with CTEPH there is a unique finding of a flow murmur overlying the lung fields caused by turbulent flow through partially obstructed or recanalized pulmonary arteries.

Diagnosis

Though most patient present with progressive dyspnoea and exercise intolerance, CTEPH is not often suspected and there may not even be an awareness of this condition amongst clinicians. Therefore, the diagnosis of CTEPH is often delayed. More common conditions such as coronary artery disease, chronic obstructive airway disease, asthma or interstitial lung disease are suspected and evaluated. These investigations eventually reveal pulmonary hypertension which is then further investigated.

Pulmonary function test—spirometry is often normal. However there may be a mild restrictive (due to parenchymal scaring) or obstructive pattern seen. Diffusion capacity is reduced out of proportion to any spirometry abnormalities.

Chest radiograph may be normal or it may show enlargement of the main pulmonary arteries with attenuation of the peripheral vessels resulting in oligemic lung fields, diminished retrosternal space from right ventricular enlargement, and prominent right heart boarder due to right atrial dilatation. Pleural effusions may also be seen as the disease progresses.

Figure 1—CXR showing mild cardiomegaly, enlarged central pulmonary arteries, prominent right heart boarder.

Ventilation-perfusion (V/Q) lung scan is said to be central to the diagnosis of CTEPH. A normal scan rules out both acute and chronic PE. It has a greater sensitivity for CTEPH over computerised tomography pulmonary angiography (CT-PA) [9].

Transthoracic echocardiogram (TTE) is the test that usually first suggests pulmonary hypertension, with increased tricuspid regurgitant velocity and estimated pulmonary pressures. Right atrial enlargement and right ventricular hypertrophy with reduced systolic function may be apparent. There may also be leftward displacement of the septum, which could result in impairment of left ventricular filling and function.

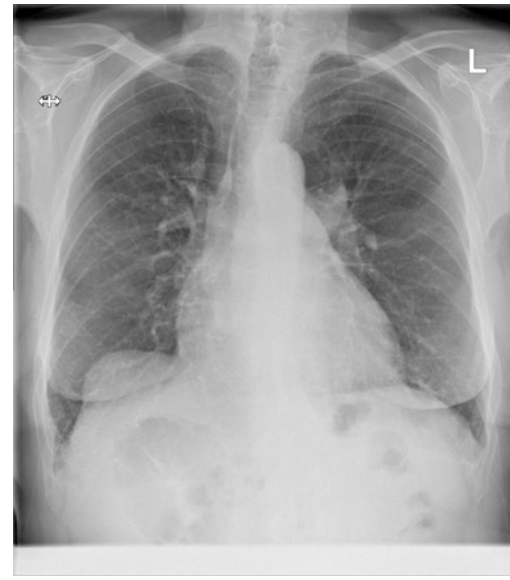

Fig. 1 Chest X-ray of a patient with chronic thromboembolic pulmonary hypertension

Pulmonary angiography had previously been the "gold standard" imaging modality for the evaluation of operability in CTEPH. Certain angiographic patterns are associated with the presence of thromboembolic material—pouch defects, webs or bands, intimal irregularities, tapering and narrowing of the major arteries, and branch obstruction. However, the value of this investigation is operator dependent as expertise for performing and interpreting pulmonary angiograms is essential. Since other modalities such as CTPA and MRI angiography have become more readily available, these are now favoured over conventional pulmonary angiography in some centres.

Computed tomographic pulmonary angiography (CT-PA) can demonstrate right ventricular enlargement, chronic thromboembolic material within the pulmonary arteries, bronchial artery collateral flow and mosaic attenuation of the lung parenchyma. It is the most common imaging modality used to assess patients with possible CTEPH and to assess operability.

Magnetic resonance angiography (MRA) can be used to visualise the pulmonary vascular tree and assess right ventricular size and function.

Right heart catheterization is necessary for the diagnosis of pulmonary hypertension. Cardiac output and PVR can then be calculated.

Coronary angiogram—as part of the work up for surgery a coronary angiogram is recommended for patients above 40–45 years of age or patients with symptoms of chest pain or significant risk factors.

Management

Untreated, the prognosis of CTEPH is poor with severe debilitating symptoms. Lifelong anticoagulation is essential in all patients and is primarily used to prevent recurrent embolic events and to limit the development of thrombus in regions of low flow within the pulmonary vasculature.

Medical management—the pulmonary artery pressure and vascular resistance may be lowered with the use of pulmonary vasodilators and remodelling agents. These can provide symptomatic relief but the treatment effects are relatively modest and are in no way curative. The indications for medical management include patients who are being bridged to surgery, patients who have residual pulmonary hypertension following surgery and those who are not candidates for surgery.

Surgical management—Pulmonary endarterectomy (PEA) is the definitive therapy for CTEPH and is potentially curative. The decision for operative management is based upon several patient factors. Ideally all patients should be referred to a specialist centre with expertise in CTEPH for formal assessment. Within the UK all patient diagnosed with CTEPH are referred to a national multi-disciplinary meeting for clinical assessment. This team includes: physicians (respiratory and cardiology), radiologists and surgeons.

Balloon pulmonary angioplasty—is the newest treatment in recent years for CTEPH. Its role is still evolving and it is likely to have some overlap with PEA. However there is currently no long-term data on its outcomes.

Patient Selection for Pulmonary Endarterectomy

The decision on operability is complex and based upon several criteria:

- Amount of disease present and the distribution within the pulmonary vasculature.
- The severity of pulmonary hypertension and whether the level correlates with the disease pattern and the number of segments affected.
- The co-morbidities of the patients so that surgical risk can be assessed.
- The willingness of the patient to undergo major surgery.

Surgical Technique

The objective of PEA surgery is to remove all of the obstructions within the pulmonary arteries, reduce the PVR and facilitate reverse remodelling of the right heart. Even though the amount and pattern of disease has already been assessed pre-operative by radiological imaging, the true extent of the disease can only be determined intra-operatively.

The approach for PEA is through a median sternotomy incision. Cardiopulmonary bypass (CPB) is instituted with ascending aortic and bi-caval cannulation. Vents are inserted in the pulmonary trunk and the left ventricle via the right superior pulmonary vein. The patient is systemically cooled to 20 °C. Bilateral pulmonary endarterectomies are performed via incisions in the intrapericardial right and left pulmonary arteries along their lengths anteriorly. There is usually a fair amount of bronchial collateral blood flow into the pulmonary artery lumen and in order to perform a distal subsegmental dissection, a good surgical headlight and a bloodless field is required. To achieve the latter, periods of cardioplegic arrest and deep hypothermic circulatory arrest (DHCA) are utilised, with intervening 10-minute systemic re-perfusion intervals for every 20 minutes of DHCA or when cerebral oxygen saturations fall below 35%.

A number of specialised instruments are utilised in order to perform the surgery (Fig. 2): A—Beaver 6900 Mini-Blade (Beaver Visitec International, Inc. MA, USA), B—Jamieson dissecting aspirator (Millenium Surgical Instruments), C—Watson Cheyne dissector, D—Modified Adson retractor, E—Long tissue forceps, F–I—Madani DeBakey Forceps both short and long, with fine (1 mm) and broad (2.5 mm) tips (Wexler Surgical, Tx, USA). Figure 3 demonstrates a close up of the tip of the Jamieson dissecting aspirator with its smooth rounded edges to prevent trauma and four side apertures in additional to the opening at the end to maximise its effectiveness in clearing blood from the operating field.

Typically, the right pulmonary artery dissection is performed first. Figure 4 shows the incision of the right pulmonary artery with the Adson retractor separating the aorta and superior vena cava. The dissection starts by identifying the correct endarterectomy plane within the media of the arterial wall. Care must to be taken not to be in too deep a plane, risking perforation or too shallow, which would result in a thinned out specimen and an incomplete clearance. A Beaver Mini-Blade is used to make a shallow incision on the inside surface of the pulmonary artery (Fig. 5). A dissection plane is developed with the Watson Cheyne dissector. The ideal plane leaves behind a pearly white smooth surface and is the easiest dissection plane to propagate. Figure 6 illustrates the Jamieson dissecting aspirator extending the dissection plane. The endarterectomy specimen is dissected distally into the subsegmental branches. Figure 7 shows the specimen being removed from the subsegmental branches. On completion of the endarterectomy, CPB is resumed and the patient re-perfused while the arteriotomy is closed and preparation made for endarterectomy of the left pulmonary artery. Figure 8 displays a view inside the pulmonary artery once the dissection has been completed demonstrating the pearly white smooth surface that is left behind. When PEA has been completed on both sides, the patient is rewarmed and weaned from CPB.

The classification of chronic thromboembolism (CTE) is based on an intra-operative classification system that categorises the patients according to the surgical specimen type. This has recently been refined (Table 1) [10]. An example of a PEA specimen is shown in Fig. 9.

Post-operative Management

Post-operatively all patients are managed in the critical care area where they continue to be closely monitored. This should include: 3 lead ECG, pulse oximetry, invasive arterial and venous pressures, invasive pulmonary artery pressures, end-tidal CO_2 and body temperature.

The emphases are careful management of the right ventricle and minimising the pulmonary vascular resistance. The goals are to ensure that there is adequate systemic oxygen delivery and the avoidance of reperfusion pulmonary oedema. This is usually achieved by judicious fluid management and the use of inotropic agents as guided by thermodilution cardiac output studies and mixed venous oxygen saturations.

Outcomes

Given the magnitude and complexity of the operation, operative mortality is gratifyingly low in specialist centres. University of California San Diego (UCSD) where PEA surgery was developed is the most experienced centre world-wide, with a reported mortality rate of 2.2% in their most recent series, [11] compared to a 5.2% mortality in their previous cohort. This highlights the importance of centre experience and shows that there is a significant learning curve to master patient selection and the peri-operative management.

Even though operative mortality is low there are several specific complications to PEA surgery that can be catastrophic if not managed appropriately:

Reperfusion lung injury—this can manifest within a few hours of surgery with

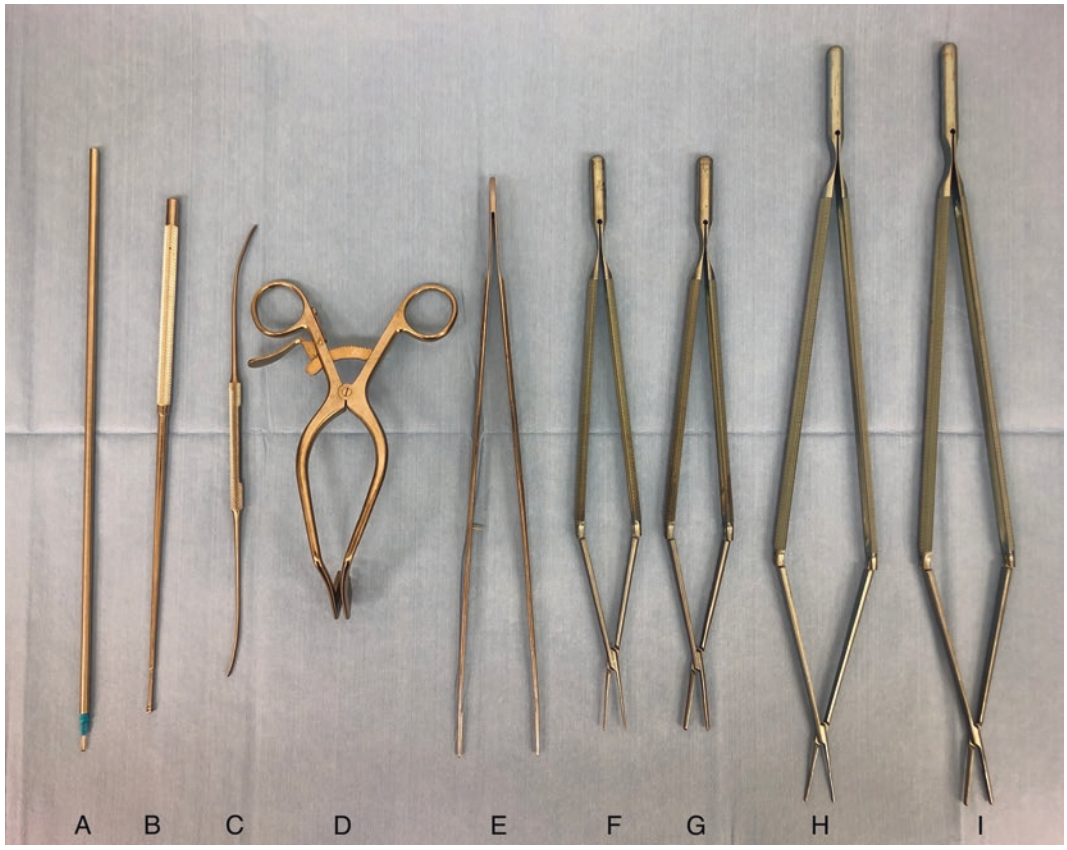

Fig. 2 Specialist instruments for pulmonary thromboendarterectomy

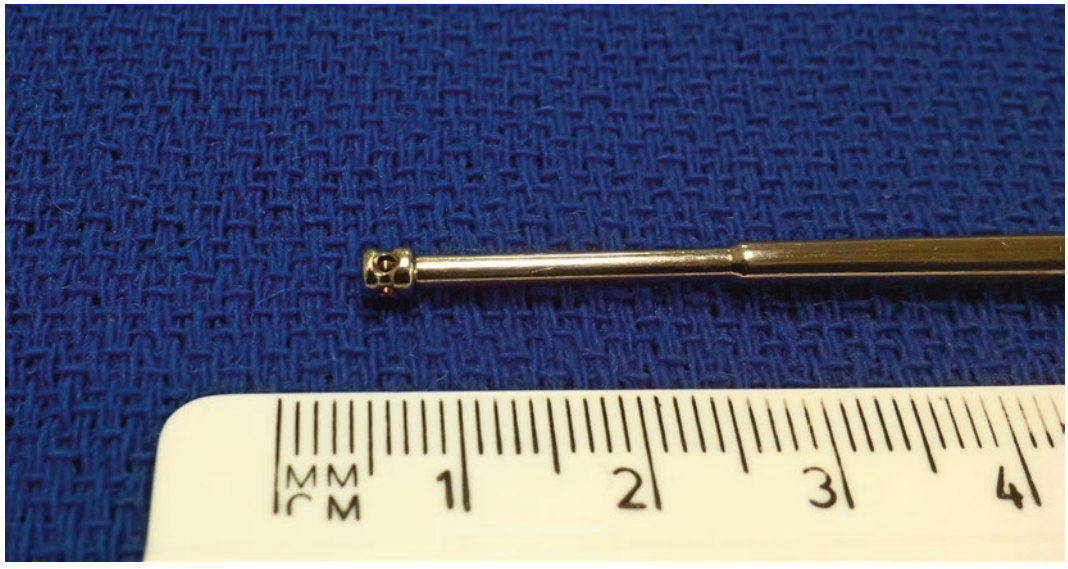

Fig. 3 Close-up view of the Jamieson dissector aspirator

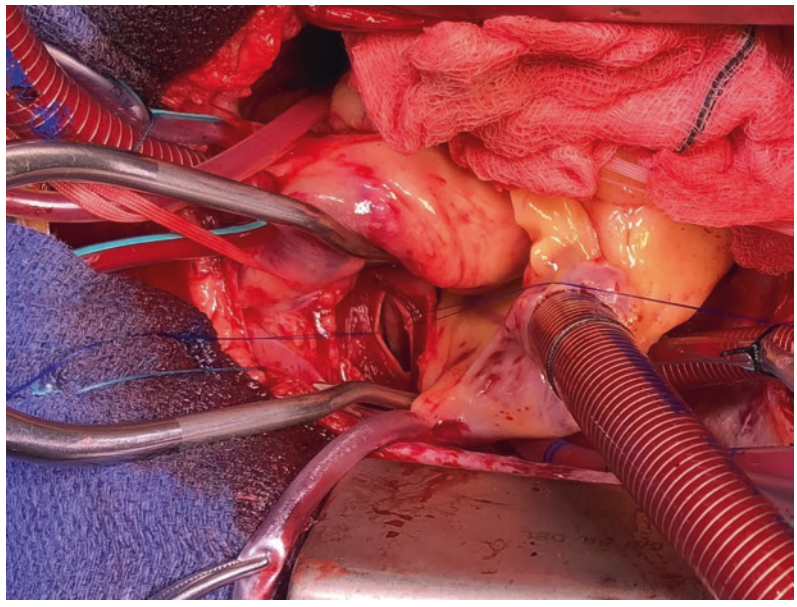

Fig. 4 Incision in the right pulmonary artery in between the ascending aorta and the superior vena cava

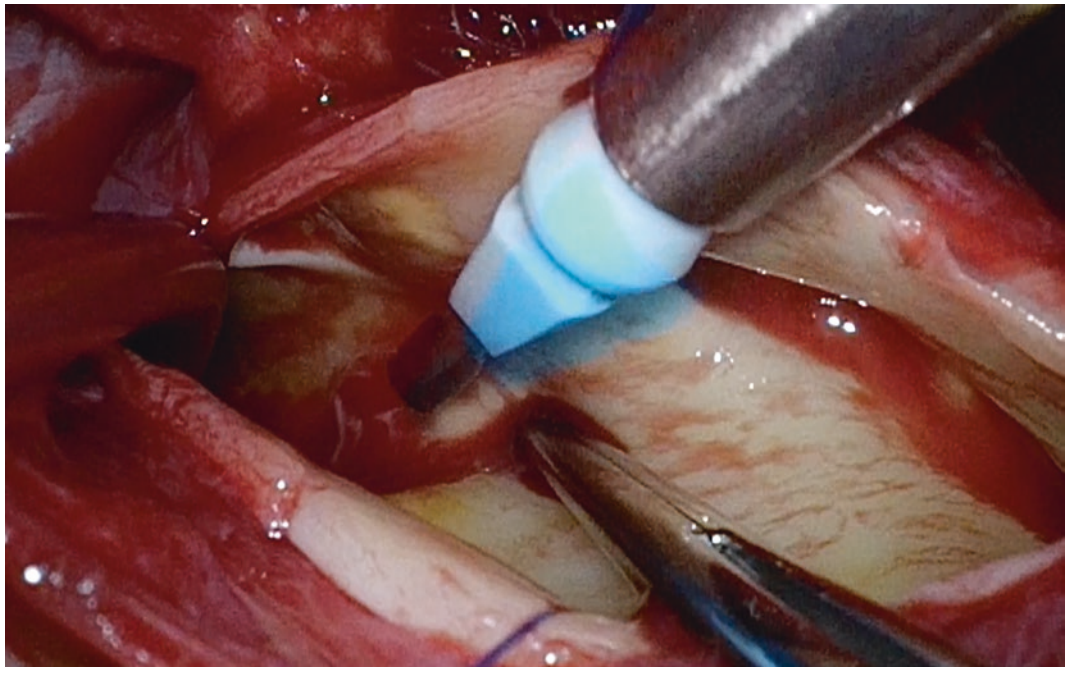

Fig. 5 Shallow incision on the inside surface of the pulmonary artery with the Beaver Mini-Blade

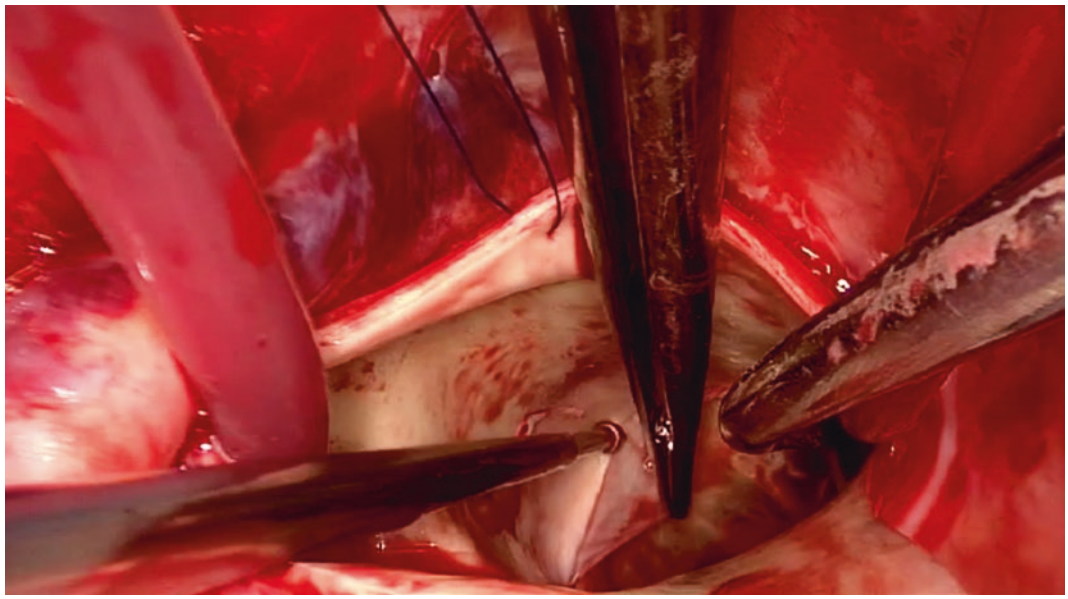

Fig. 6 Progressing the endarterectomy plane with the Jamieson dissector aspirator

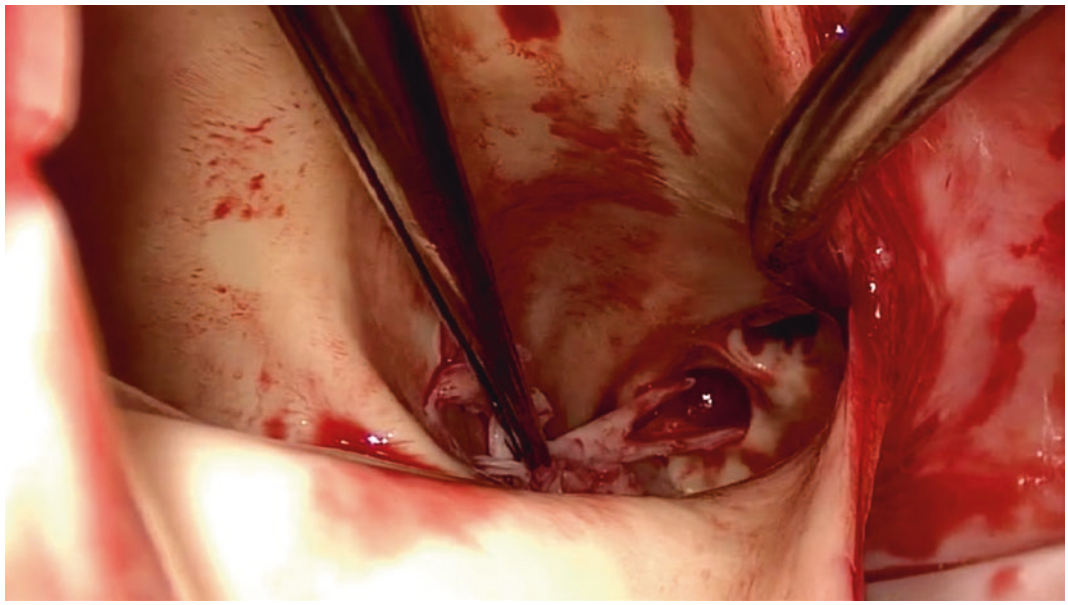

Fig. 7 The endarterectomy specimen showing a bifurcation fibrous cast from the pulmonary artery segmental branches

worsening oxygenation. Several measures can be taken to reduce the incidence of reperfusion injury including minimum fluid infusion to provide adequate preload for acceptable cardiac output and oxygen delivery, diuresis, maintenance of the haematocrit levels and lung protective ventilation. In severe cases, early veno-venous extra-corporeal membrane oxygenation (ECMO) may be necessary to support the patient while the reperfusion injury settles.

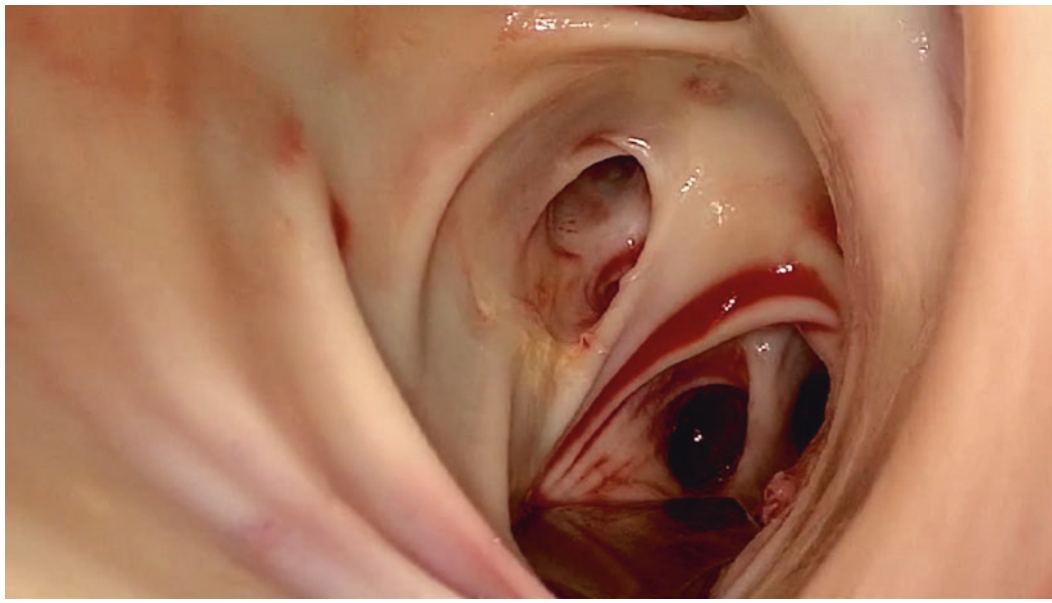

Fig. 8 A view of the inside of the endarterectomised pulmonary artery showing widely patent openings to segmental branches

Table 1 University of California San Diego chronic thromboembolism (CTE) surgical classification

Surgical levels	Location of CTE
Level 0	No evidence of thromboembolic disease in either lung
Level 1	CTE starting in the main pulmonary arteries
(Level IC)	(Complete occlusion of one main pulmonary artery with CTE)
Level II	CTE starting at the level of lobar arteries or in the main descending pulmonary arteries
Level III	CTE starting at the level of the segmental arteries
Level IV	CTE starting at the level of the subsegmental arteries

Airway bleed—Bleeding into the airways can be dramatic and typically becomes apparent when the right ventricle is allowed to fill and eject. This is a result of a breach of the pulmonary arterial wall during endarterectomy. A relatively small amount of blood in the airway can generate frothing and difficulties with ventilation resulting in hypoxia and haemodynamic instability when attempting to wean from CPB. The only viable option in this setting is conversion of CPB to central veno-arterial ECMO, reversal of the systemic heparinisation and any coagulopathy. Sometimes, it is necessary to stop ventilation and clamp the endotracheal tube to contain the bleed. Once bleeding into the airways has stopped, bronchoscopy is performed to clear out the blood clots in the airways under direct vision. Ventilation is gently resumed and when adequate tidal volumes are achieved without excessive peak airway pressures, attempts at weaning from ECMO can be trialled. This is a serious complication and carries a mortality of around 50%.

Residual pulmonary hypertension—this can result from either inadequate surgical clearance or the presence of distal vasculopathy. This may lead to unstable haemodynamics in

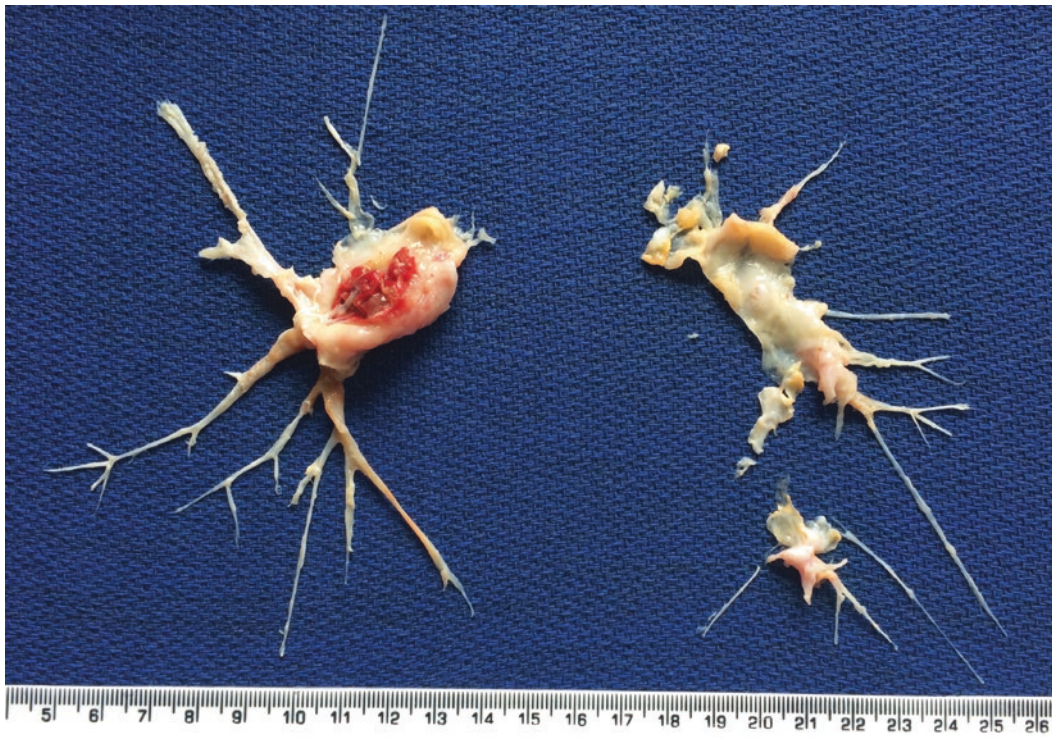

Fig. 9 Example of a PEA specimen

Table 2 Baseline and post PEA surgery patient haemodynamics, functional capacity and exercise tolerance [12]

	Preoperative	Postoperative	*P* value
FC 1/2/3/4, %	0/9/68/23	38/47/15/0	<0.0001
mPAP, mmHg	47 ± 11	27 ± 10	<0.0001
PVR, dynes·s·cm^{-5}	830 ± 382	317 ± 239	<0.0001
6MWD, m	260 ± 126	353 ± 118	<0.0001

the early postoperative period that may require veno-arterial ECMO support.

In most patients there is a significant improvement in haemodynamic variables postoperatively, with associated improvements in functional capacity and exercise tolerance. Table 2 show results from a recent study of 880 patients who had PEA surgery. Survival rates at 1, 3,

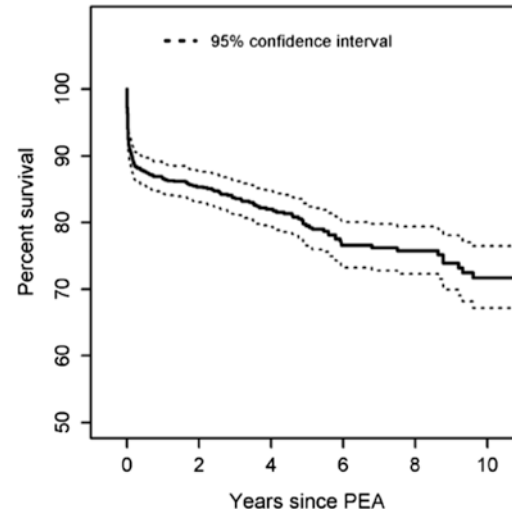

Fig. 10 Kaplan-Meier curve showing percent survival post-PEA surgery [12]. Figure used with permissions

5- and 10-years post PEA have been shown to be 86%, 84%, 79% and 72% respectively. Figure 10 shows the percentage survival from this study. Recurrent CTEPH is rare and 49% of deaths in the long term are unrelated to CTEPH [12].

Conclusion

Severe pulmonary hypertension is a serious condition with a poor prognosis. For patients with CTEPH, timely referral to a specialist pulmonary hypertension centre and thorough diagnostic workup provide the best guidance for their appropriate management.

Pulmonary endarterectomy surgery is a potentially curative treatment for CTEPH. In high volume experienced centres, the operative mortality is low. With the development of ECMO support, it is now potentially possible to salvage the more serious complications of PEA and further improve operative survival. In correctly selected patients, PEA surgery can provide significant long-term symptomatic and prognostic benefits.

Self-study

1: Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as pre-capillary pulmonary hypertension with:

A. Central venous pressure (CVP) < 10 mmHg
B. Mean pulmonary artery pressure (mPAP) > 25 mmHg,
C. Pulmonary capillary wedge pressure (PCWP) > 15 mmHg
D. Pulmonary vascular resistance (PVR) < 2 Wood units

2: The most common presenting symptom in patients with CTEPH is:

A. Chest pain
B. Dyspnoea
C. Peripheral oedema
D. Syncope

3: Which one of these investigations would rule out CTEPH:

A. An abnormal CT-PA
B. A normal coronary angiogram
C. A normal CXR
D. A normal ventilation-perfusion (V/Q) lung scan

Answers

1. B
2. B
3. D

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Thoracic Traumas —General Aspects

Alessio Campisi, Luca Bertolaccini, and Franco Stella

Key Points

- Thoracic traumas are one of the leading causes of death, especially in young people
- Essential is to remember the ABCDE assessment to direct the primary survey
- Most blunt chest traumas can be treated conservatively
- Penetrating traumas are often fatal, so proper and immediate diagnosis is mandatory for those patients who survive until the arrival of the paramedics
- When surgery is indicated, the doctor should decide fast

Introduction

Trauma is a worldwide pandemic and one of the leading causes of death and disability. Estimation of its epidemiology is a demanding and challenging task, because of the lack of global data. In the United States, injuries represent the fourth leading cause of death over all ages and the leading cause of death among people under 44 years old [1]. In 2003, 164,002 U.S. residents died from trauma [2].

Trauma care is of importance to all medical and surgical specialists; thus, all medical figures should be aware that injuries differ regarding causes, the types of injury, severity and prognosis. Therefore, it is essential to know about the trimodal distribution of death due to trauma. Almost 50% of deaths occur within seconds to minutes after injury, usually, due to massive bleeding or severe neurologic injury. The second peak of death amounts for 20–30% of passing, occurs within minutes to several hours after the injury and it is due to progressive neurologic, cardiovascular, or pulmonary compromise; especially during this period, organised trauma care could improve the chance of survival of the patient. The final third peak of death (10–20%) occurs several days to weeks after initial injury, usually secondary to infections and multiorgan system failure [3, 4].

Chest trauma represents a prominent part of injuries, especially regarding mortality being second only to head trauma as a cause of death in injured patients and accounting for 25% of all trauma mortality [1]. Thus, physicians working in trauma centres must be prepared to make quick decisions and to deal with them.

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Primary Survey

The primary survey is essential to rapidly identify life-threatening conditions in order to prevent death. Patients are assessed, and their treatment priorities are established, based on their injuries, vital signs, and injury mechanisms.

A simple mnemonic (ABCDE) is used to direct the primary survey:

- **A**irway with cervical spine control;
- **B**reathing and ventilation;
- **C**irculation and haemorrhage control;
- **D**isability and neurologic assessment;
- **E**xposure/Environmental control.

The main goal of this algorithm is to avoid distractions by obvious injuries and to identify life-threatening conditions in a prioritised sequence based on the effects of the injuries on the patient's physiology. This sequence exposes the greatest threat to life, which is addressed first [5].

Airway with Cervical Spine Control

In the initial evaluation of a trauma patient, the airway should be assessed first to ensure patency while protecting the cervical spine and to identify any causes of airway obstruction (foreign bodies, facial, mandibular or tracheal/laryngeal fractures etc.). Initially, the chin-lift or jaw-thrust manoeuvre is recommended to achieve airway patency. Conscious patients should be asked to open their mouth, which should be inspected, and then to talk.

Airway control in the conscious patient can be achieved with an easily inserted nasopharyngeal trumpet; on the contrary, an oropharyngeal airway is used in the unconscious patient. Definitive control of the airway, with eventual ventilation and oxygenation of the patient, are obtained with endotracheal intubation via the nasal or oral route. An airway should be established surgically if intubation is contraindicated or cannot be accomplished.

Breathing and Ventilation

Airway patency alone does not ensure adequate ventilation. Thus, once airway patency is established, the patient's ability to breathe must be assessed. A regular function of the lungs, chest wall and the diaphragm are necessary for ventilation and gas exchange to occur.

Each component must be rapidly examined and evaluated. Injuries that severely impair ventilation in the short term include tension pneumothorax, flail chest with pulmonary contusion, massive haemothorax, and open pneumothorax. These injuries need to be identified during the primary survey and treated promptly (see further on for each disease).

Every injured patient should receive supplemental oxygen through the orotracheal tube if intubated or through a mask-reservoir device if not. The pulse oximeter should be used to monitor oxygen haemoglobin saturation.

Circulation and Haemorrhage Control

Circulatory compromise in trauma patients can result from many different injuries. Hypotension in the trauma patient is caused by blood loss until proven otherwise. The elements of clinical observation that yield valuable information in hypovolemic patients within seconds are level of consciousness, skin colour, and pulse. In the case of significant haemorrhage with hypovolemia, the level of consciousness is reduced due to low cerebral blood flow; the skin is ashen and pale, the pulse is rapid and thread.

The source of bleeding should be identified as either external or internal. External bleeding can usually be defined and controlled by direct manual pressure, avoiding tourniquets when possible because of the risk of distal ischemia. The major areas of internal bleeding are the chest, abdomen, retroperitoneum, pelvis, and long bones. The source of the bleeding is usually identified by physical examination and imaging. Management may include chest decompression with a pleural tube, pelvic

binders and surgical intervention. Definitive control is traditionally performed during the second survey.

Disability and Neurologic Assessment

Rapid neurologic evaluation is performed at the end of the primary survey. This evaluation establishes the patient's level of consciousness (using the Glasgow Coma Scale), pupillary size and reaction, lateralizing signs, and spinal cord injury level.

An altered level of consciousness may be caused by decreased cerebral oxygenation and/or perfusion, or it may be caused by direct cerebral injury. Traumatic injuries may cause damage to the central and peripheral nervous systems. Spinal cord injuries happen most commonly in the cervical and lumbar regions; the rigidity of the bony thorax protects the thoracic spine. A rapid assessment of disability and neurologic function is of primary importance to prevent further neurologic injury.

Exposure/Environmental Control

The patient should be completely undressed, to examine the entire body and assess any injuries. Complete exposure, usually by cutting off his or her garments, allows the identification of entry and exit wounds, extremity deformities, contusions, or lacerations. After the examination, the patient should be covered with warm blankets or an external warming device to prevent hypothermia.

Emergency Department Interventions

Thoracic trauma has a high mortality rate. Many patients with thoracic trauma die right before or just after reaching the hospital; however, many of these deaths could be prevented with prompt diagnosis and treatment. In those patients, once adequate oxygenation and ventilation have been established, the primary resuscitation effort must rule out other life-threatening chest injuries such as pneumothorax, haemothorax and pericardial tamponade.

Pneumothorax

Pneumothorax is defined by the presence of air in the intrapleural space, with subsequent lung collapse (Fig. 1). From an etiopathological point of view, a pneumothorax can be classified as spontaneous and non-spontaneous (Iatrogenic and Traumatic). Pathophysiologically, it can be classified as open, closed (simple) and tension.

A simple pneumothorax is created when a tear in the pleura allows entry of air into the pleural space with resultant loss of negativity in intrathoracic pressure. It's usually secondary to blunt trauma, but it can be caused by penetrating injuries damaging the lung too.

In the case of pneumothorax, breath sounds are usually decreased on the affected side, and percussion may demonstrate hyperresonance. Expiratory chest X-ray or echography aid in the diagnosis. A small, asymptomatic pneumothorax may be treated with observation and rest; otherwise, insertion of a chest tube should be performed. Neither general anaesthesia nor positive-pressure ventilation should be administered in a patient who has sustained a traumatic pneumothorax or who is at risk for unexpected intraoperative tension pneumothorax until a chest tube has been inserted because the risk for conversion to a tension pneumothorax is high.

Open pneumothorax is characterised by direct communication between the chest cavity and the environment. In penetrating chest injuries, if the size of the chest wall injury reaches two-thirds of the diameter of the trachea, air passes preferentially through the chest wall defect with each respiratory effort, impairing effective ventilation and leading to hypoxia and hypercarbia. Open pneumothorax will generally require chest wall repair. The timing of it depends on whether the defect can be controlled, its size, and the severity of the patient's other injuries. Therefore, initial management is

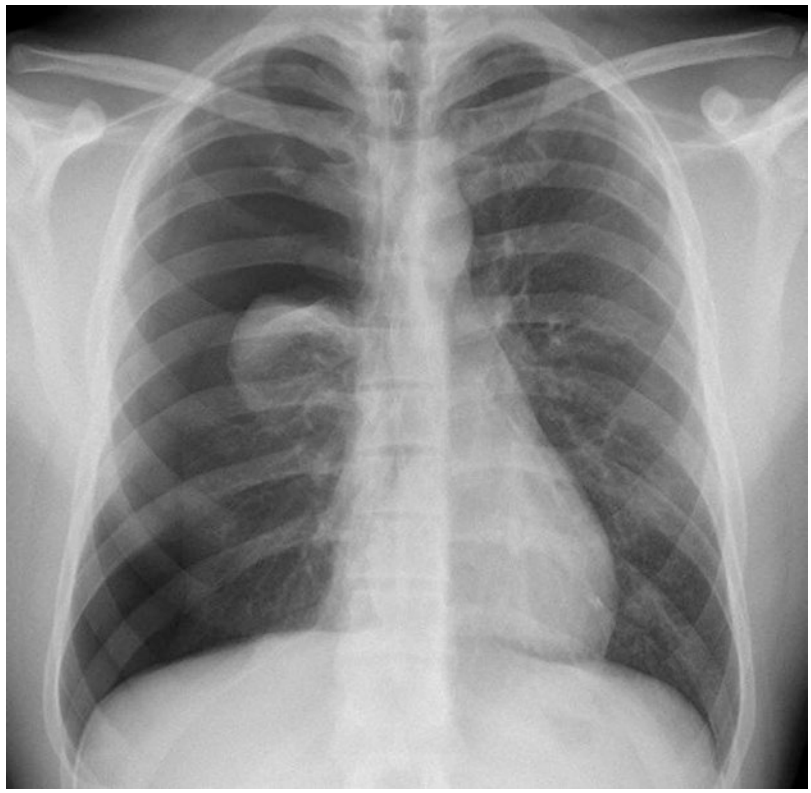

Fig. 1 Right Pneumothorax on a Chest X-ray

accomplished by promptly closing the defect with a sterile occlusive dressing, immediately followed by placement of a chest tube.

Tension pneumothorax develops when a "one-way valve" air leak occurs from the lung or through the chest wall. Air accumulates into the pleural space, resulting in complete lung collapse, contralateral displacement of the mediastinum, decreased venous return impairing the cardiac output and eventually causing cardiac arrest. The diagnosis of tension pneumothorax should always be considered in a patient with penetrating chest trauma. It is less likely to occur after blunt trauma. However, the most common cause of tension pneumothorax is mechanical ventilation with positive-pressure ventilation in patients with a visceral pleural injury.

Clinical findings in case of tension pneumothorax are hypotension, and tachycardia, absent breath sounds on the affected side, tracheal deviation to the opposite side, neck vein distention and cyanosis.

Tension pneumothorax requires immediate decompression, initially by the insertion of a large needle into the second intercostal space in the midclavicular line of the affected hemithorax and afterwards by the introduction of a chest tube [5].

Haemothorax

Haemothorax is defined by the presence of fluid in the pleural cavity with a haematocrit higher than 25–50% of the patient's blood. Both blunt and penetrating injuries may be associated with it, but it is far more common after a penetrating injury. A haemothorax can be defined as moderate, if there are less than 1500 ml of fluid, or massive if it is more than 1500 ml (Fig. 2). The primary cause of

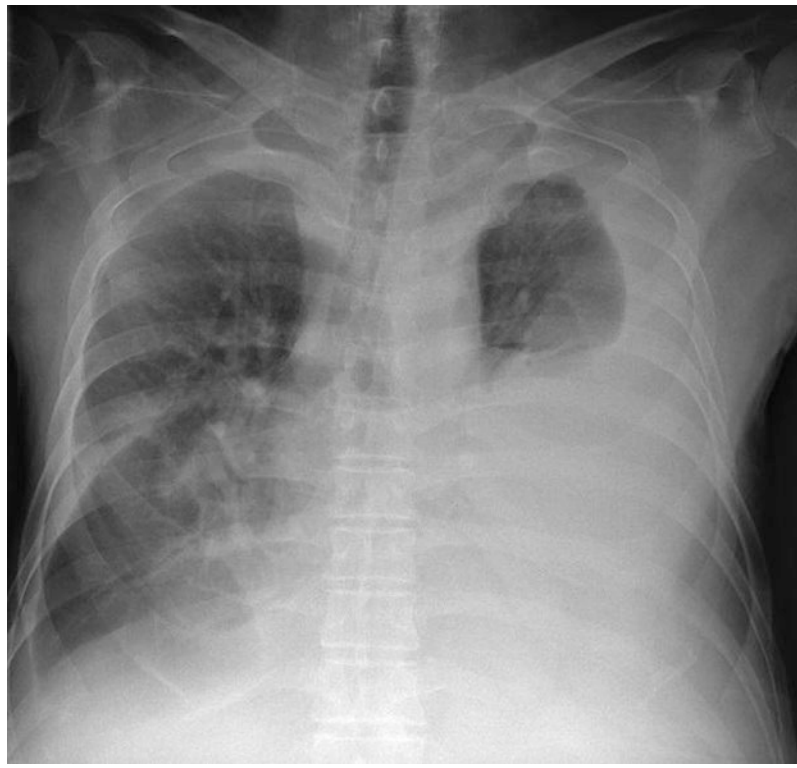

Fig. 2 Massive left haemothorax after blunt trauma

the former case is usually lung laceration or laceration of an intercostal vessel or internal mammary artery, a massive haemothorax more often occurs secondary to a penetrating wound that disrupts the systemic or hilar vessels.

On physical examination, there is the absence of breath sounds over the injured hemithorax and dullness to percussion; in case of massive haemothorax, signs of shock and hypoxia may be found.

For the most common type of haemothorax, that is usually self-limiting, the first approaches are the insertion of a large-bore (36 Fr or greater) chest tube and blood volume replacement (even with autotransfusions with blood from the chest tube). If the first blood removed from the chest is >1,500 mL, or if ongoing blood loss is 200 mL/hr for at least 2–4 hours, or if repeated blood transfusions are needed, the patient should be explored in the operating room for haemorrhage control. The ultimate decision for surgery is based on the patient's hemodynamic status.

Cardiac Tamponade

Cardiac tamponade is a life-threatening condition in which blood accumulates in the pericardium (Fig. 3). The pericardial sac is a relatively fixed fibrous structure, so a relatively small amount of blood can interfere with cardiac activity, reducing venous return to the heart, dropping its filling and cardiac output, eventually leading to circulatory collapse. Cardiac tamponade may develop slowly or may occur rapidly, requiring prompt diagnosis and rapid intervention. The diagnosis is suggested by Beck's triad of hypotension, distant heart sounds, and elevated central venous pressure. Echocardiogram focused

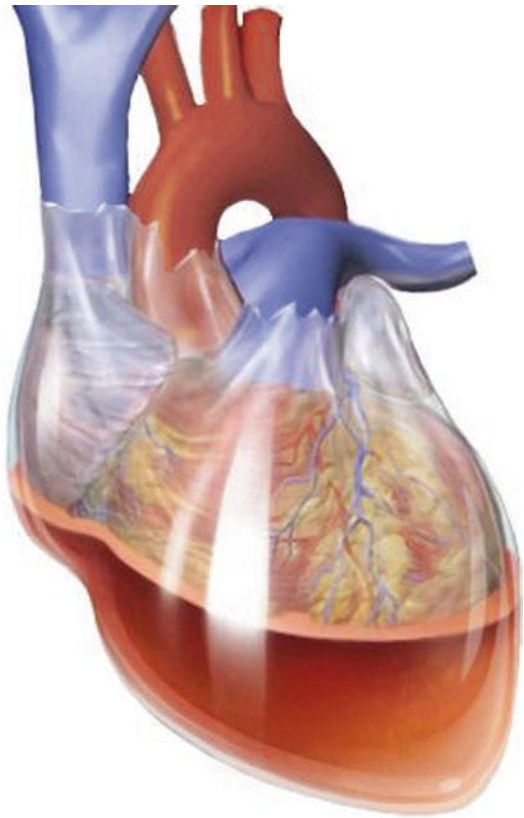

Fig. 3 Cardiac Tamponade (https://en.wikipedia.org/wiki/File:Blausen_0164_CardiacTamponade_02.png)

assessment sonography in trauma (FAST), or pericardial window help with the diagnosis. Pericardiocentesis with the aspiration of 10–20 ml of blood or insertion of a flexible catheter can temporarily restore normal hemodynamics, buying time for everyone to prepare for surgery. These patients should generally be considered for surgery in the operating room to diagnose and repair any sources of the bleeding [5].

Emergency Room Thoracotomy

In the severely injured, hypotensive patient, a physician, sometimes, needs to ask himself whether to perform thoracotomy in the emergency department as a life-saving manoeuvre. The decision to perform it is a difficult one and requires different considerations. In the case of penetrating injuries and pulseless patients but with myocardial electrical activity, there may be an indication for emergency thoracotomy. This procedure is rarely indicated in patients without vital signs (reactive pupils, spontaneous movement, or organised ECG activity) since the success rate in resuscitating these individuals is almost vain. Emergency thoracotomy permits evacuation of hemopericardium, direct control of intrathoracic haemorrhage, open cardiac massage, cross-clamp of the descending aorta to increase perfusion of brain and heart during simultaneous blood replacement (Fig. 4). Despite the value of these manoeuvres, the usefulness of emergency thoracotomy is still under debate, in fact, multiple papers report survival rates less than 10 percent, others a more favourable prognosis [6].

Secondary Survey

The secondary survey begins when the ABCs have been assessed, and resuscitation has been initiated. It involves a complete physical examination to identify additional injuries, an upright chest X-ray if possible, arterial blood gas analysis (ABGA), and pulse oximetry as well as ECG monitoring. The final phase of acute trauma care is instituting definitive treatment, that may vary from observation of the patient to complex surgery.

Blunt Trauma

Blunt traumas to the chest can injure any of the components of the chest wall and organs in it. They usually are caused by direct injuries, but also rapid deceleration and other mechanisms can cause damage to chest organs. In Western Countries, motor vehicle crashes, pedestrians hit by vehicles, falls or violence, are responsible for most blunt thoracic traumas.

Clinical presentation depends on the mechanism of trauma, the involved organs and associated extrathoracic injuries.

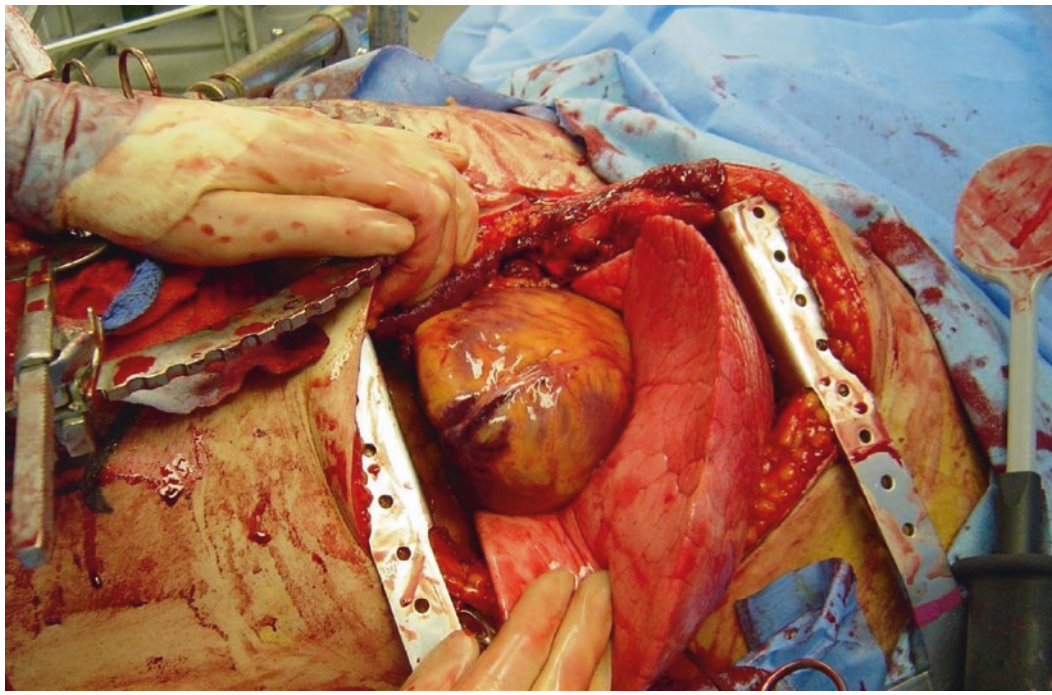

Fig. 4 Emergency room thoracotomy (https://en.wikipedia.org/wiki/File:Emergency_Thoracotomy.png)

Tracheobronchial Injuries

Injury to the trachea or a major bronchus is rare but potentially a fatal condition. It is usually associated with simultaneous injuries to adjacent structures such as the great vessels (especially the descending thoracic aorta), oesophagus, manubrium etc.

Most tracheobronchial injuries occur within 2.5 cm of the carina, secondary to sudden deceleration either because of a motor vehicle accident or a fall, causing the trachea or bronchi to be completely disrupted. Most patients do not reach the hospital in time, and those who do have a high mortality rate and often need surgery. Signs and symptoms on physical examination depend on the type of injury; patients typically present with subcutaneous emphysema, difficulty speaking, respiratory distress, pneumothorax or haemoptysis (Fig. 5). Bronchoscopy confirms the diagnosis and the location of the lesion. In case of suspected injury to the cervical or mediastinal trachea, intubation should be obtained beyond the injury, possibly under direct bronchoscopic guidance. In patients with unilateral bronchial injury, temporary intubation of the opposite mainstem bronchus may be required.

Treatment is expectant or operative depending on the nature and severity of the injury.

Pulmonary Contusion

Pulmonary contusion is the disruption of alveolar-capillary interfaces and subsequent accumulation of blood and protein in the interstitium and alveoli. It occurs during blunt traumas secondary to transmission of kinetic energy (with or without overlying rib fractures and subsequent laceration) to the lung parenchyma. Patients may be asymptomatic or present with rapidly developing severe hypoxia and the need for mechanical ventilation, depending on the extent of the injury and the need for volume replacement that aggravates the process. In addition to associated injuries, pre-existing medical conditions such as chronic obstructive pulmonary disease, heart failure and renal failure greatly influence the course of patients

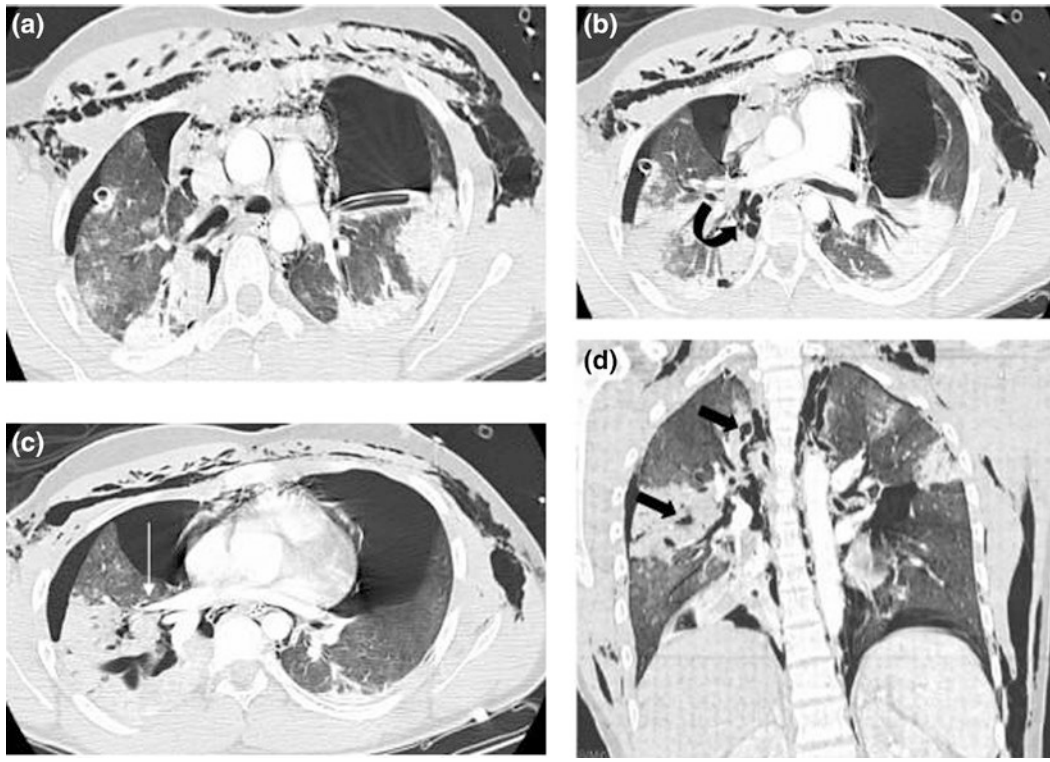

Fig. 5 Traumatic complete disruption of the right main bronchus (https://en.wikipedia.org/wiki/File:Bronchial_rupture.jpg)

with pulmonary contusions, increasing the risk for hypoxia with the need for intubation and mechanical ventilation.

Initial chest radiographs may be normal or only show small nodular patchy changes, but severe contusions may present as frank consolidation involving a significant part of the lung parenchyma. If there are substantial changes shortly after injury, in general, the course will be severe. Chest CT scans can define the degree more accurately and detect occult changes not seen on chest X-rays (Fig. 6).

The treatment is generally supportive: oxygen is often needed, restricted intravenous fluids to avoid volume overload and diuretics (in a stable patient), optimal pain control. Intubation is performed for the usual indications. A significant early complication is a pneumonia, and intubation increases its rate; nevertheless, there is no indication for prophylactic antibiotic therapy.

Blunt Cardiac Injury

The exact definition of blunt cardiac trauma is difficult because it is not one single entity but rather includes a spectrum of cardiac injuries. Blunt cardiac trauma can result in myocardial muscle contusion, cardiac chamber rupture, coronary artery dissection and/or thrombosis, or valvular disruption.

Any mechanism that transfers kinetic energy to the heart may cause injury so that it may occur secondary to compression, deceleration, blast, direct forces applied to the chest (even after closed cardiopulmonary resuscitation).

Clinical presentation may range from chest discomfort to complete hemodynamic instability and cardiopulmonary arrest. Similarly, cardiac rupture typically presents with cardiac tamponade.

Diagnostic modalities include chest X-ray, electrocardiogram (ECG), measurement of cardiac enzymes, echocardiography. Early use

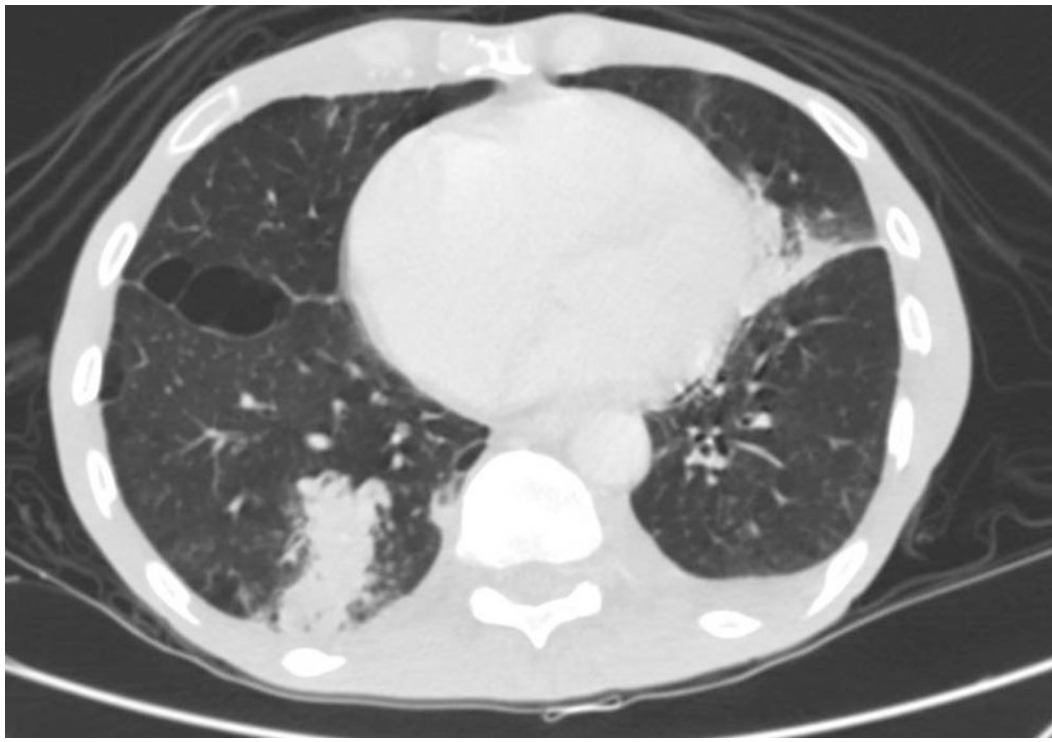

Fig. 6 Pulmonary Contusion of the right lower lobe

of FAST can facilitate diagnosis. The electrocardiographic abnormalities detected by ECG are variable and may range from sinus tachycardia, atrial flutter and atrial fibrillation, to ventricular tachycardia and ventricular fibrillation, bundle-branch block (usually right), and ST-segment changes. The presence of a normal ECG in a hemodynamically stable patient warrants no further investigation, on the contrary, unstable patients or patients with an abnormal ECG should be monitored for the first 24 hours. The presence of positive cardiac troponins can be diagnostic of myocardial infarction, but their use in diagnosing blunt cardiac injury is inconclusive.

Therapy depends on the nature and the severity of the injury and the subsequent damage.

Traumatic Aortic Disruption

More than 90% of thoracic great vessel injuries are due to penetrating trauma. Blunt traumas could cause lesions but require tremendous energy to produce them, so they are usually traumas due to falls or high-speed frontal impacts.

Traumatic aortic rupture is a common cause of sudden death after those kinds of accidents. It usually involves disruption of the aorta just distal to the ligamentum arteriosum. Patients with aortic rupture who have a chance of survival tend to have an incomplete laceration of the vessel or a contained hematoma. This lesion should be suspected in the appropriate clinical circumstances because specific signs and symptoms are frequently absent. History may direct the diagnosis, together with some adjunctive radiologic signs on chest X-ray: widened mediastinum, loss of aortic knob contour, nasogastric tube deviation to the right (if present), deviation of the trachea to the right, first or second rib fracture, or pleural cap (accumulation of blood above the pleura), left haemothorax. Aortography contrast computed tomography (CT), or transoesophageal echocardiogram can be used in diagnosis.

If there is even a slight suspicion of aortic injury, the patient should be evaluated for surgery in a qualified centre. The treatment is either primary repair or resection of the torn segment and replacement with an interposition graft. Endovascular repair is nowadays an acceptable alternative approach (Fig. 7).

Rib Fractures and Flail Chest

The ribs are the most commonly injured component of the thoracic cage, occurring in about 10% of chest traumas and 20% of severe injuries. They are relatively uncommon in childhood thanks to the flexibility of the rib cage, and the risk increases with age secondary to osteoporosis.

Rib fractures can be caused by a direct and focal application of force, leading to internal displacement of the rib and lesion of the inner part of the bone (fracture en dedans) or by an anteroposterior force (crushing trauma), leading to an increase of the external curvature of the bone and lesion of its outer cortical part (fracture en dehors).

Clinically, rib fractures may be almost asymptomatic or may present with manifestations ranging from pain on motion to pneumonia secondary to splinting and hypoventilation. On physical examination, point tenderness or a ridge may be present over the fracture site.

Chest X-ray is usually the first radiological exam done, primarily to exclude other intrathoracic injuries and not just to identify rib fractures, which could be missed, especially fractures of the anterior cartilages or separation of the costochondral junctions. CT scan may provide better documentation of other associated injuries, but circumstances indicate it.

The management of rib fractures may vary from bed rest, optimal pain control (oral, intravenous therapy or epidural catheter) and aggressive pulmonary toilet to major surgery (fixation with pericostal sutures around or through the ribs, plates, wires, Judet staple etc.).

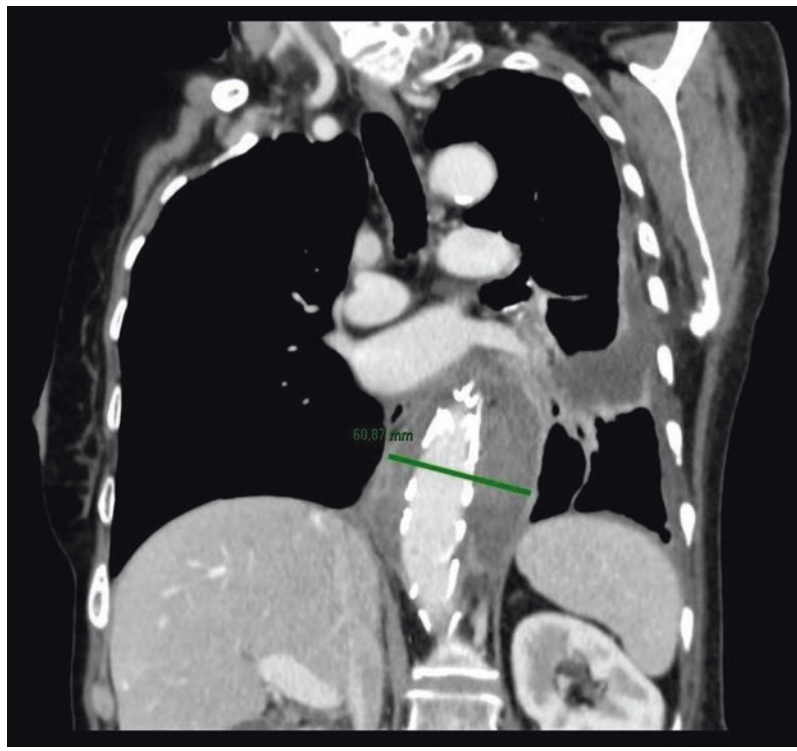

Fig. 7 Traumatic aortic disruption: Endovascular repair

Moreover, the therapeutic approach depends on which ribs and how many of them are injured.

Fracture of the upper ribs (1–3) requires significant force and can be associated with major vascular or nerve injury (the subclavian vessels and the brachial plexus). Because of the severity of the associated injuries, mortality may be as high as 35%. An arteriogram is mandatory in case of abnormalities in pulse or the neurologic examination of the upper extremities. Fractures of the middle ribs (4–9) are the most common ones because of their exposure and lack of muscular protection; they may be associated with a lung contusion, extrapleural hematoma (differential diagnosis with pleural effusion), haemothorax and pneumothorax. Fractures of the lower rib cage (10–12) are rare because of their flexibility and are frequently seen in association with liver or splenic injuries.

Flail chest occurs when at least three ribs are fractured in two or more points creating a part of the chest wall that moves independently with respiration (Fig. 8). During paradoxical motion of the chest cavity, when the patient inhales, the flail segment collapses, following the decreased intrathoracic pressure. In contrast, on expiration, the flail segment is pushed out. Thus, flail chest may result in dramatic impairments of lung function (rebreathing of the airway with following dead-space abnormality) and is in principle a life-threatening condition.

Flail segments are most common in the anterior and anterolateral chest and are more common in the mid to lower part of the chest wall, and the reasons are multiple. First, the percentage of anterior traumas, second, the exposure of

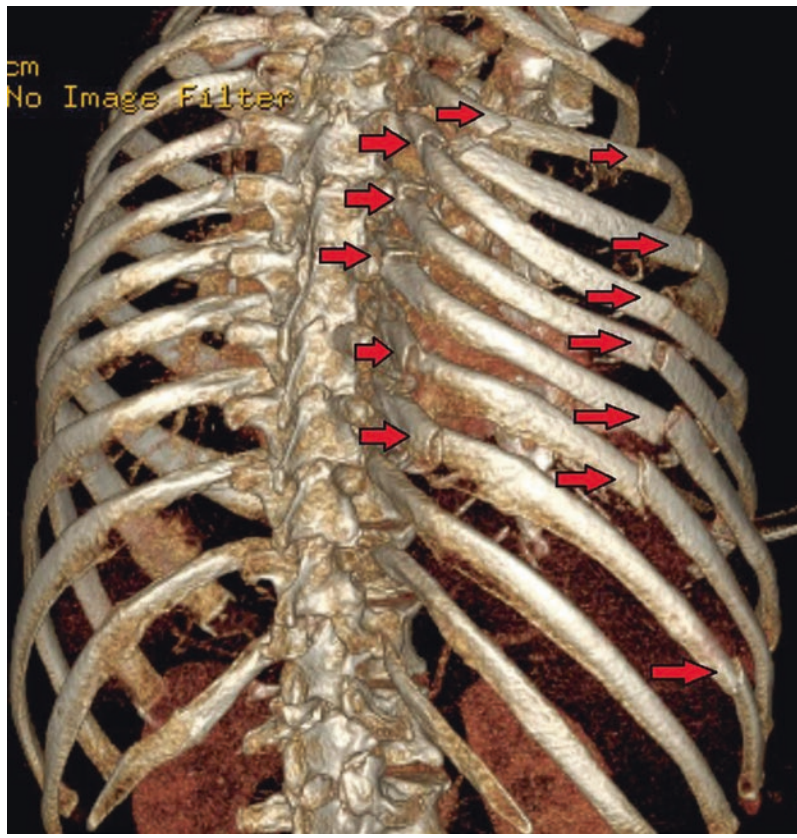

Fig. 8 Posterior Flail Chest (https://en.wikipedia.org/wiki/File:Flailchest3to9.png)

the mid-lower rib cage and third, the support of the large dorsal muscles.

Although Chest X-rays often show the multiple fractures, flail chest is first of all a clinical and not a radiological diagnosis. The force of the injury required is high and often causes a significant lung contusion, which worsens gas exchange. Treatment of pain with rib blocks may improve ventilation. Intubation will allow lung expansion for the same reason as for open pneumothorax.

Thanks to the better knowledge of the pathophysiological mechanism, the treatment of flail chest has changed over the years. Current treatment aims at avoiding intubation and mechanical ventilation unless it is strictly necessary. Management is, once again, directed to aggressive pain control, even with continuous epidural analgesia, and pulmonary toilet. Anyhow, surgical fixation may be required for incompletely disrupted segments of the chest wall.

Sternal Fractures

Sternal fractures usually occur during motor vehicle accidents secondary to direct impact of the anterior chest against steering wheels or the dashboard. In almost 20% of cases, another severe injury to the chest wall is observed, especially single or multiple costochondral dislocations, eventually resulting in flail chest. Moreover, there is an association with severe intrathoracic injuries such as myocardial contusion or rupture, aortic or bronchial disruption, lesions to the vertebral column or with extrathoracic ones, particularly to the skull. Isolated sternal injuries are relatively rare, because the high energy required to break it, usually transfers to other organs nearby.

Sternal fractures are most often transverse and occur at the junction of the manubrium and the sternal body (Fig. 9).

Patients, when alert, complain of pain. On physical examination, chest wall deformity and ecchymosis or abrasion of the skin overlying the sternum may be seen; palpation may reveal point tenderness or a ridge. Sternal fractures are difficult to detect on anterior or oblique films, so in case of suspicion, a lateral chest X-ray is suggested. A CT scan is rarely needed.

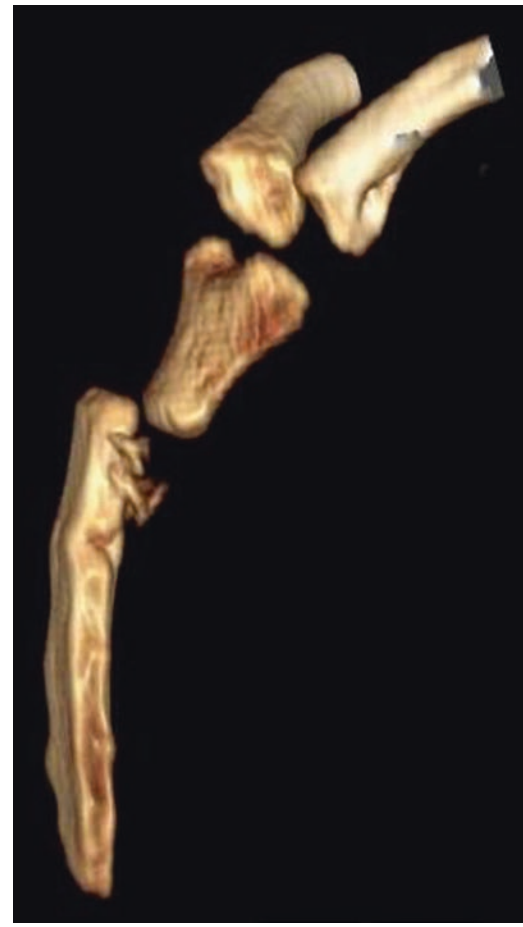

Fig. 9 Transverse Sternal Fracture at the at the junction of the manubrium and the body. CT scan reconstruction

Simple undisplaced sternal fractures require no treatment. Complex fractures with overlapping fragments may require surgery with reduction, debridement, and fixation.

Diaphragmatic Injuries

Diaphragmatic injuries may occur from penetrating or blunt trauma. Almost 75% of injuries are secondary to blunt traumas and 25% secondary to penetrating ones. Usually, injuries arising after blunt mechanisms tend to produce more substantial defects than penetrating traumas. Left-sided lesions are more commonly seen during clinical practice, probably because of the shock-absorbing effect of the liver on the right side. In case of blunt traumas, the

general mechanics responsible for diaphragmatic rupture is a direct anterior blow to the abdomen that increases the intra-abdominal pressure significantly, causing the damage. Another possibility is a lateral blow that may detach the fibres of the diaphragm from the chest wall. Patients may present with symptoms that are abdominal or thoracic or both. They may present with chest or abdominal pain, dyspnoea, and orthopnoea, nausea and vomiting.

Moreover, a diaphragmatic injury is often associated with damage to other organs such as rib fractures, myocardial contusions, abdominal organ rupture or wounds of the chest and abdomen etc. Diagnosis is not always easy to make, because history as well as physical examination lack both, sensitivity and specificity. Chest X-ray is the most valuable simple test, but immediately after trauma, diaphragmatic injuries are frequently missed, especially when the chest film shows an elevated diaphragm, acute gastric dilatation or loculated hemopneumothorax. If a laceration of the left diaphragm is suspected, a gastric tube should be inserted to identify it on the chest X-ray. CT scan is a second level imaging choice and may help recognise small ruptures, identify any organ herniation and eventually associated lesions (Fig. 10). MRI is helpful in equivocal cases but rarely needed. Treatment depends on the extent of the injury as well as the time of diagnosis. Nevertheless, all diaphragmatic injuries should be repaired, either with direct suture or with prosthetic mesh, because there is a high risk for complications such as incarceration, possible strangulation and pulmonary compression. Abdominal approach (either by laparoscopy or laparotomy) is suggested in cases of acute herniation secondary to abdominal trauma; on

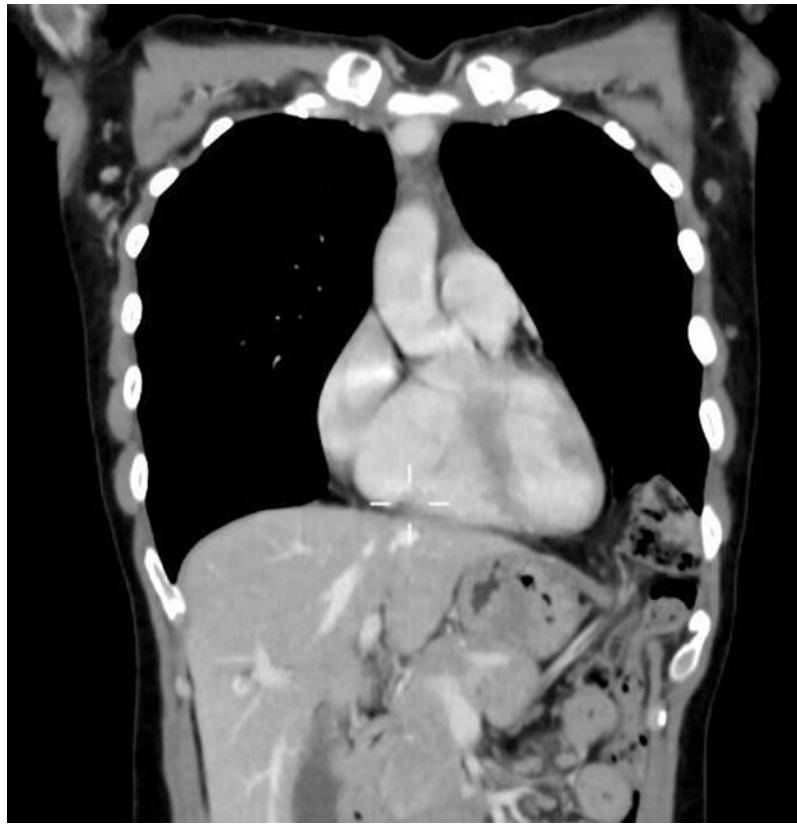

Fig. 10 Left diaphragmatic injury with delayed herniation of descending colon and greater omentum

the contrary, a transthoracic surgery (open or minimally invasive) is recommended in cases of delayed rupture [7].

Traumatic Asphyxia

Traumatic asphyxia, or crushing injury to the chest, is a medical emergency resulting from severe thoracic trauma. A rare condition occurs when a powerful compressive force is applied to the thoracic cavity of a patient during Valsalva manoeuvre. Exhalation against the closed glottis leads to a sudden increase of the intrathoracic pressure causing venous backflow from the right atrium into the valveless veins of the neck and the head. Findings associated with a crush injury to the chest include oedema, cyanosis and petechiae of the upper torso, neck and face (Morestin's Mask) and bilateral conjunctival haemorrhage (Fig. 11). Massive swelling and even cerebral oedema may be present. Diagnosis is usually clinical, and the treatment is primarily supportive. This condition is often associated with injuries to other organs that require treatment as well.

Penetrating Trauma

The knowledge about penetrating trauma comes from the management of military injuries experienced over the centuries. Nowadays, the likelihood of penetrating chest traumas is high in developing countries and in those where the general population has free access to handguns.

Penetrating injuries are the result of the application of a mechanical force to a restricted area; thus, the magnitude of damage depends on the type of weapon, site of entry and direction of the weapon or bullet. For stab wounds, the injury depends on the type and length of the instrument; moreover, rotation of the weapon increases the severity of the injury. Nevertheless, survival is better in stab traumas compared to gunshot wounds. The latter usually cause

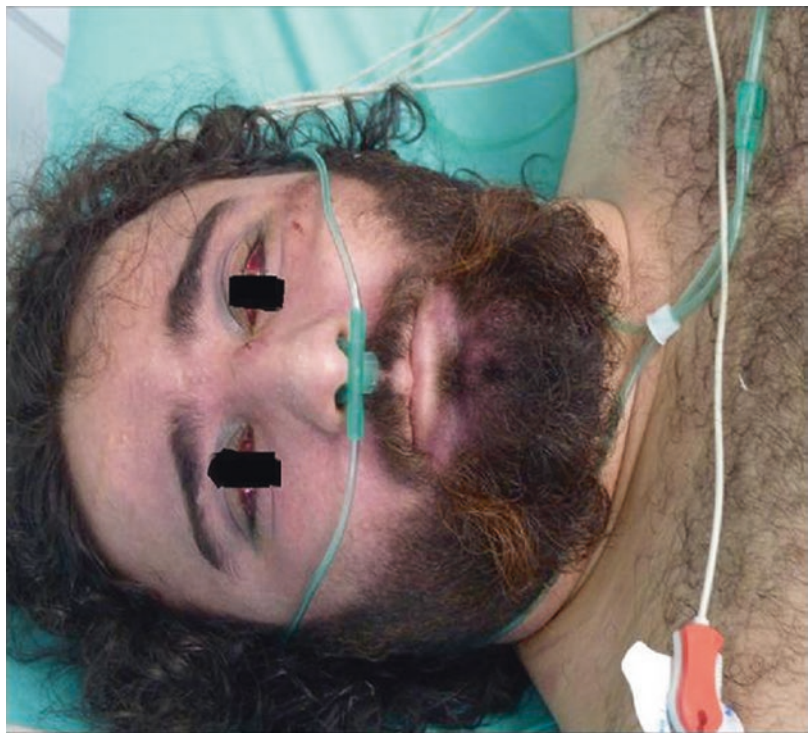

Fig. 11 Bilateral subconjunctival hemorrhages and oedematous head, neck, and upper chest in a patient after traumatic asphyxia (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3626248/bin/CRIM.EM2013-857131.001.jpg)

visceral injury and are highly lethal. Their damage depends on the velocity and biomechanics of the projectile. The main issue is kinetic energy, and according to the formula kinetic energy = ½ * mass * velocity^2, velocity is a more critical factor than mass. The speed of the projectile may be low, medium, or high. Low-velocity projectiles have limited kinetic energy, usually causing less damage. Medium-velocity injuries include bullet wounds from handguns. High-velocity projectiles are those with a muzzle velocity of >600 m/s, which produce injury in adjacent organs in addition to that in the bullet path due to tissue cavitation, and shock waves. Another factor responsible for the damage is the structure of the bullet, accordingly its shape and deformity (i.e. jacket bullets, hollow-point bullets).

Separately discussed should be iatrogenic penetrating traumas that occur after diagnostic or therapeutic procedures such as thoracentesis, chest tube insertion, lung biopsies, liver biopsies or pericardiocentesis.

Proper and immediate diagnosis is mandatory for those patients who survive until the arrival of the paramedics. Direct deaths are usually due to massive bleeding.

Physical examination is once again the primary tool. Chest X-ray is the first radiological exam requested, and it should be obtained in every patient with a penetrating trauma of the chest. Further investigations may vary from CT scan to angiography.

Treatment depends on the involved organs and requires a good knowledge of the

trauma and expertise.

Chest Wall Injuries

Chest wall injuries account for approximately 10% of all penetrating chest traumas but rarely need intervention.

Stab wounds penetrate the chest wall but seldom cause severe damage. Gunshot wounds may damage all the tissues of the chest wall, but only close shotgun projectiles may severely injure the chest, producing a large amount of tissue loss and mutilation (Fig. 12).

In any chest wall penetrating trauma, surgeons should be aware of associated injuries, especially pneumothorax and haemothorax.

Physical examination should evaluate all signs and symptoms that may help identify any associated condition.

Chest radiography is mandatory after a primary survey.

Patient's conditions and involved organs direct the treatment to clinical observation or surgery.

Lung Injuries

The lungs occupy the entire thoracic cavity, so penetrating traumas usually injure them. Although the lung is one of the most resilient organs to penetrating trauma, its damage may be minor and localised or extensive and destructive.

Knife and low-velocity projectiles tend to create perforation and a small area of contusion. It results in air entry into the pleural space (pneumothorax) or haemothorax. Anyhow, pulmonary artery pressure usually is >25 mmHg, and the levels of tissue thromboplastin are high. Thus, persistent blood leak is uncommon, and bleeding often stops without intervention.

In the case of high-velocity projectiles, the damage of the lung itself is usually less than in other organs, thanks to the elasticity of the lung, even though it may be extensive in some cases (Fig. 13).

A severe complication of penetrating lung injury is systemic air embolization, caused by direct communication between the airway and the pulmonary venous system, leading to death if not recognised [8].

Tracheobronchial Injuries

Tracheobronchial injuries can be life-threatening. They are usually more often associated with penetrating wounds than with blunt trauma. Any part of the central airway may be involved, but cervical tracheal lacerations usually follow stab injuries. Bullet wounds generally damage the intrathoracic trachea and main bronchi. Most of these injuries are lethal before medical arrival secondary to associated injuries to major vessels.

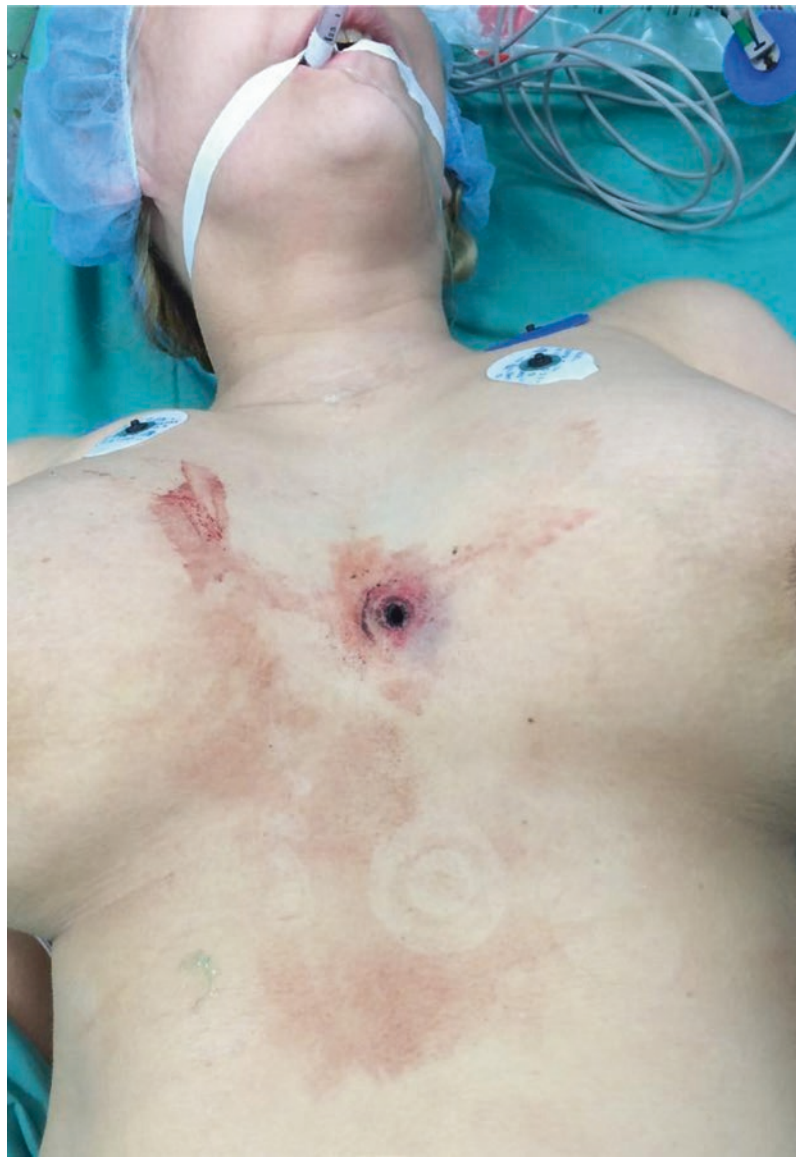

Fig. 12 Gunshot entrance wound situated in the middle third of chest bone (https://www.ncbi.nlm.nih.gov/core/lw/2.0/html/tileshop_pmc/tileshop_pmc_inline.html?title=Click%20on%20image%20to%20zoom&p=PMC3&id=4885112_gr1.jpg)

Clinical presentation depends on the size and the site of injury. Cervical tracheal damage usually presents with emphysema, haemoptysis and dyspnoea. On the other hand, a tension pneumothorax can be the first sign of an injury of the intrathoracic trachea or one of the main bronchi.

If needed, intubation should be obtained beyond the injury, possibly under direct bronchoscopic guidance, especially in case of haemoptysis to protect the lungs. Isolated and small (<50%) cervical tracheal wounds can be managed conservatively; otherwise, surgery is mandatory to save the patient's life.

Heart and Major Vessels Injuries

Penetrating cardiac injuries are a leading cause of traumatic death in urban areas. Their mortality, including pre-hospitalisation deaths, reaches

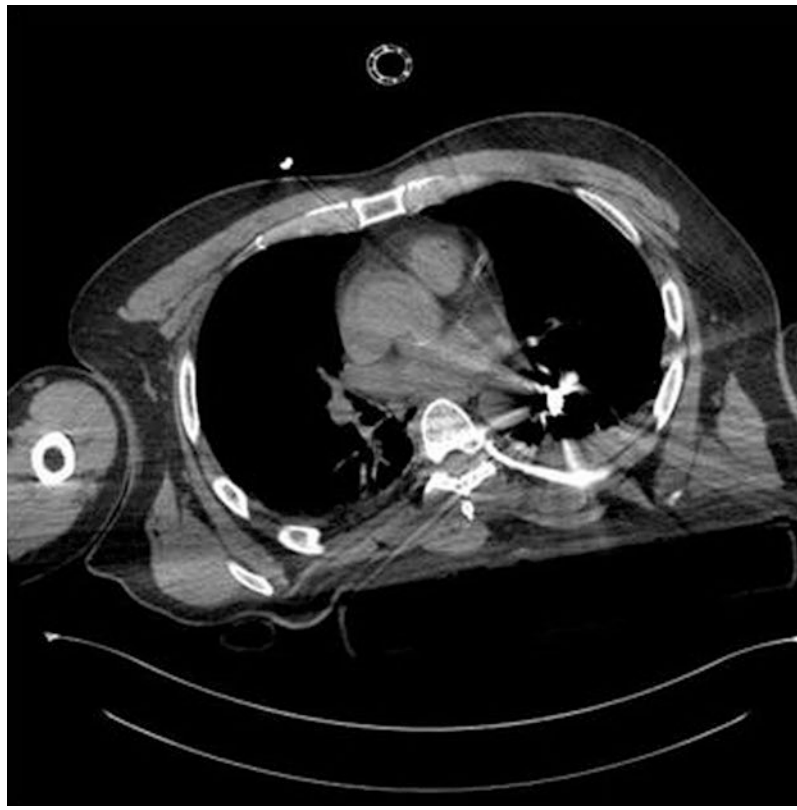

Fig. 13 Retained projectile in the left lung (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4641384/bin/13017_2015_48_Fig2_HTML.jpg)

almost 90%. Those patients arriving alive at the hospital usually have an injury to a low-pressure chamber of the heart. Pericardial tamponade can, sometimes, save the patient's life preventing massive bleeding (Fig. 14).

Diagnosis is generally easy to make.

Immediate intervention is imperative and based on the patient's hemodynamic status. This includes emergency thoracotomy and suture of the cardiac wound.

Major vascular injuries generally cause death immediately, so patients rarely reach medical facilities. Death occurs because of exsanguinating haemorrhage, massive haemothorax or pericardial tamponade. Survival injuries usually involve low-pressure systems, including pulmonary artery, vena cava, innominate or pulmonary veins. Involved vessels may be deduced from the site of the penetrating trauma. An essential diagnostic tool is the chest X-ray.

Treatment in alive patients includes pericardiocentesis, chest tube insertion, transfusion of blood, emergency thoracotomy or sternotomy and closure of the injury.

Oesophageal Injuries

Oesophageal injuries are uncommon (<1% of patients) and most of these injuries are due to penetrating trauma. The anatomical position of the oesophagus usually protects it from damage; in fact, the most commonly injured part is the cervical oesophagus. Isolated lesions are rare.

Diagnosis may be difficult due to the rarity of these injuries, the scarcity of clinical signs, and the associated injuries. The clinical presentation depends on the site of injury and the time of its identification. Dyspnoea, cyanosis, subcutaneous emphysema, pneumomediastinum, sepsis, and shock may be present. However, small perforations may heal spontaneously and may

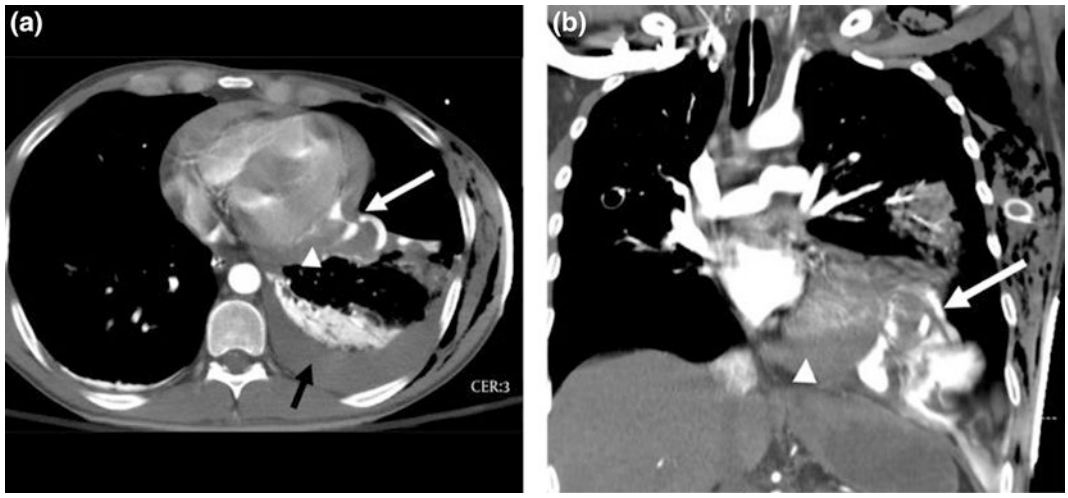

Fig. 14 CT scan of a patient with penetrating injury causing rupture of the lateral wall of the left ventricle (white arrow) with contrast extravasation causing tamponade (arrowhead) and left pleural effusion (black arrow) (https://www.ncbi.nlm.nih.gov/core/lw/2.0/html/tileshop_pmc/tileshop_pmc_inline.html?title=Click%20on%20image%20to%20zoom&p=PMC3&id=4727463_traumamon-20-19086-g001.jpg)

sometimes even go unrecognized. Large lesions can cause mediastinitis and consequent sepsis.

Early diagnosis is vital for the patient. Chest X-ray and esophagoscopy direct the clinician.

Immediate surgery with primary repair and adequate tissue buttressing is mandatory.

Conclusions

Chest traumas represent a wide problem to deal with because of high mortality and variability. Didactically, they may be divided into blunt and penetrating injuries or by area of manifestation. However, patients usually have multiple-organ lesions. Thus, complete knowledge of the pathophysiology of the trauma is required for the treating physician. Good perception and the ability to make quick and accurate decisions are essential skills for the medical staff.

Every physician who works in a trauma centre should be familiar with the optimal care of patients with chest trauma.

Exercises/Self-study

1. Which statement about clinical signs of tension pneumothorax is true?
   a. tachycardia
   b. cyanosis
   c. neck vein distention
   d. a b and c
2. Morestin's mask occurs in:
   a. Open pneumothorax
   b. multiple rib fractures
   c. traumatic asphyxia
   d. pulmonary contusion
3. Complications of the diaphragmatic injury are:
   a. incarceration
   b. strangulation
   c. pulmonary compression
   d. a b and c
4. Which statement is not true about the indication for surgery in a haemothorax:
   a. initial blood removed from the chest >1,500 mL
   b. ongoing blood loss 100 mL/hr
   c. repeated blood transfusions are needed
   d. persistent anaemia

5. Flail chest occurs when:
   a. at least three ribs are fractured in two or more points
   b. at least two ribs are fractured in one point
   c. one rib is fractured in two or more points
   d. all ribs are fractured in one point

Answers

1. Which statement about clinical signs of tension pneumothorax is true?

   a. Tachycardia represents a response to reduced venous return to the heart because of contralateral displacement of the mediastinum.
   b. Cyanosis is secondary to blood gas exchange impairment.
   c. Neck vein distention: Air accumulates into the pleural space, collapsing the lung and displacing the mediastinum contralaterally; decreased venous return occurs with neck vein distention.
   d. a, b and c.

CORRECT: D: all the mentioned are clinical findings of a tension pneumothorax.

2. Morestin's mask occurs in:

   a. Open pneumothorax: it is characterised by direct communication between the chest cavity and the environment. Clinically, patients may be tachypnoeic, dyspnoeic and tachycardic.
   b. Multiple rib fractures: manifestations range from pain on the motion to pneumonia secondary to splinting and hypoventilation.
   c. Traumatic asphyxia: secondary to a compressive force applied to the thoracic cavity of a patient during the Valsalva Manoeuvre leading to venous backflow from the right atrium into the valveless veins of the neck and the head.
   d. pulmonary contusion: if not severe, it is asymptomatic or paucisymptomatic.

CORRECT: C: Morestin's Mask presents as oedema, cyanosis, petechiae of the upper torso, neck and face and bilateral conjunctival haemorrhage after traumatic asphyxia.

3. Complications of the diaphragmatic injury are:

   a. Incarceration: herniated tissue becomes trapped and cannot quickly be moved back into place.
   b. strangulation: absent blood flow in an obstructed intestinal portion
   c. pulmonary compression: external impairment of pulmonary expansion
   d. a b and c

CORRECT: D: all the mentioned are possible complications of an unrecognised diaphragmatic injury

4. Which statement is not true about the indication for surgery in a haemothorax:

   a. Initial blood removed from the chest>1,500 mL: A haemothorax can be defined as moderate if there are less than 1500 ml of fluid, massive if it is more than 1500 ml.
   b. Ongoing blood loss of 100 mL/hr: stable patients with less than 200 mL/hr blood loss do not need surgery.
   c. repeated blood transfusions are required: persistent anaemia occurs, meaning blood loss is still ongoing.
   d. Persistent anaemia: blood loss is still ongoing, even in a patient clinically stable.

CORRECT: B: a, c and d are indications for surgery. The other indication is ongoing blood loss of 200 mL/hr for at least 2 to 4 hours.

5. Flail chest occurs when:

   a. At least three ribs are fractured in two or more points: this condition creates a part of the chest wall moves independently with respiration.
   b. At least two ribs are fractured in one point: no part of the chest cavity moves for its own.
   c. one rib is fractured in two or more points: the involved area is not enough to create a paradoxical movement of the cavity.
   d. All ribs are fractured in one point: no part of the chest cavity moves for its own.

CORRECT: A. Flail chest occurs when at least three ribs are fractured in two or more points creating a part of the chest wall moves independently with respiration.

Conflict of interest: none declared

Fund: none reported

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Blunt Thoracic Traumas

Alessio Campisi, Luca Bertolaccini, and Franco Stella

Key Points

- Adequate analgesia is essential after blunt chest trauma
- Conservative therapy and lung preservation techniques, if surgery is mandatory, are suggested
- Pleural injuries are often treated with chest tube insertion
- Primary repair of oesophageal injuries should be done as soon as possible
- All diaphragmatic injuries should be repaired

Introduction

The first description of chest injuries dates back to 1600 before Christ. Still, they are one of the leading causes of death over all ages [1, 2].

Blunt traumas can affect every component of the chest cavity and its organs. Mortality is high, and many patients do not even reach the hospital in time; for those lesions occurring within minutes to several hours after the trauma, organised trauma care could reduce the rates of death. Chest injuries due to blunt traumas are the second most common diagnosis in polytraumatized patients [2].

Mechanism of blunt trauma varies from a direct hit to rapid acceleration-deceleration, and the clinical presentation depends on the trauma mechanism and the organs involved. Considering the force required for these traumas, they are often accompanied by abdominal, head, pelvic and extremity injuries.

In this chapter, blunt thoracic traumas are discussed, focusing on their surgical management.

Pleural Injuries

Haemothorax

Haemothorax is the presence of blood in the pleural space. It occurs after both, blunt and penetrating injuries. In the former, haemothorax is found in 30–50% of patients [3]. Haemothorax is usually the result of lung damage or laceration of an intercostal vessel or internal mammary artery; systemic or hilar vessels are rarely sources of bleeding after blunt traumas.

Treatment of haemothorax depends on the quantity of blood and the patient's clinical

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condition. Less than 300 ml of intrathoracic blood does usually not require any intervention. If the patient with a moderate haemothorax is hemodynamically stable, the first approach is the insertion of a large-bore (36 Fr or greater) chest tube and blood volume replacement; the lung re-expansion allows visceral-parietal pleural apposition and bleeding tamponade. The drain is usually inserted at the level of the nipple (fourth intercostal space) behind the lateral border of the pectoralis major muscle (anterior axillary line), paying attention to anaesthesia (local and systemic if needed) and sterility.

Nevertheless, up to 30% of patients treated with chest tube insertion may have retained blood clots in the pleural space, resulting in empyema and fibrothorax with pulmonary trapping [4]. Surgery for these patients is indicated, and nowadays, improvements in video-assisted thoracoscopic surgery (VATS) enable to consider it the gold-standard therapy; in fact, it is highly effective, mainly if early performed (within 5–7 days after trauma), and it is associated with low morbidity. The goals of surgery are clot removal, bleeding control and decortication, if necessary (Fig. 1).

Moreover, the patient should be explored in the operating room for haemorrhage control if the initial blood volume removed from the chest is >1,500 mL, or if ongoing blood loss is 200 mL/hr for at least 2–4 hours, or if repeated blood transfusions are needed (Advanced Trauma Life Support guidelines).

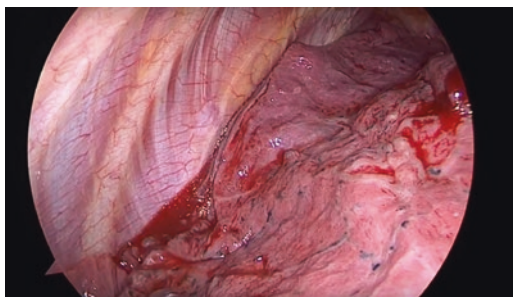

Fig. 1 Videothoracoscopic view of a right Haemothorax after chest trauma with a single rib fracture

Pneumothorax

Pneumothorax is defined by the presence of air in the intrapleural space, with subsequent lung collapse (Fig. 2). It can be the result of blunt or penetrating trauma. Lung laceration with air leakage is the most common cause of pneumothorax resulting from blunt trauma. Although rarely, a tension pneumothorax may develop after blunt traumas.

Pneumothorax may be treated in multiple ways. A small, asymptomatic pneumothorax may be treated with observation and rest, though chest tube drainage remains the most common treatment. It can be inserted through either the second intercostal space in the midclavicular line or the fourth or fifth intercostal space in the anterior axillary line.

A single chest tube often resolves the issue, but if persistent air leak is present, adjusting or adding chest drains, slurry pleurodesis with autologous blood [5], weaning from the ventilator, or changing the type of ventilation may allow healing of the laceration. Surgery, when needed, consists of resection of any damaged lung areas, usually using endostaplers or suture any lacerations and physical pleurodesis (Fig. 3). VATS is the most common approach in these patients, not forgetting that thoracotomy, preferentially a muscle-sparing one, may be necessary in selected cases.

Lung Injuries

Pulmonary Contusion

Pulmonary contusion is a common consequence of acceleration-deceleration or crush injuries. It is the result of disruption of alveolar-capillary interfaces with subsequent interstitial and alveolar oedema, haemorrhage, and alveolar collapse. Pulmonary contusions can occur as isolated injuries or associated with other injuries and have an elevated overall mortality rate.

Its incidence depends on the method of diagnosis, being elevated in both, blunt and penetrating

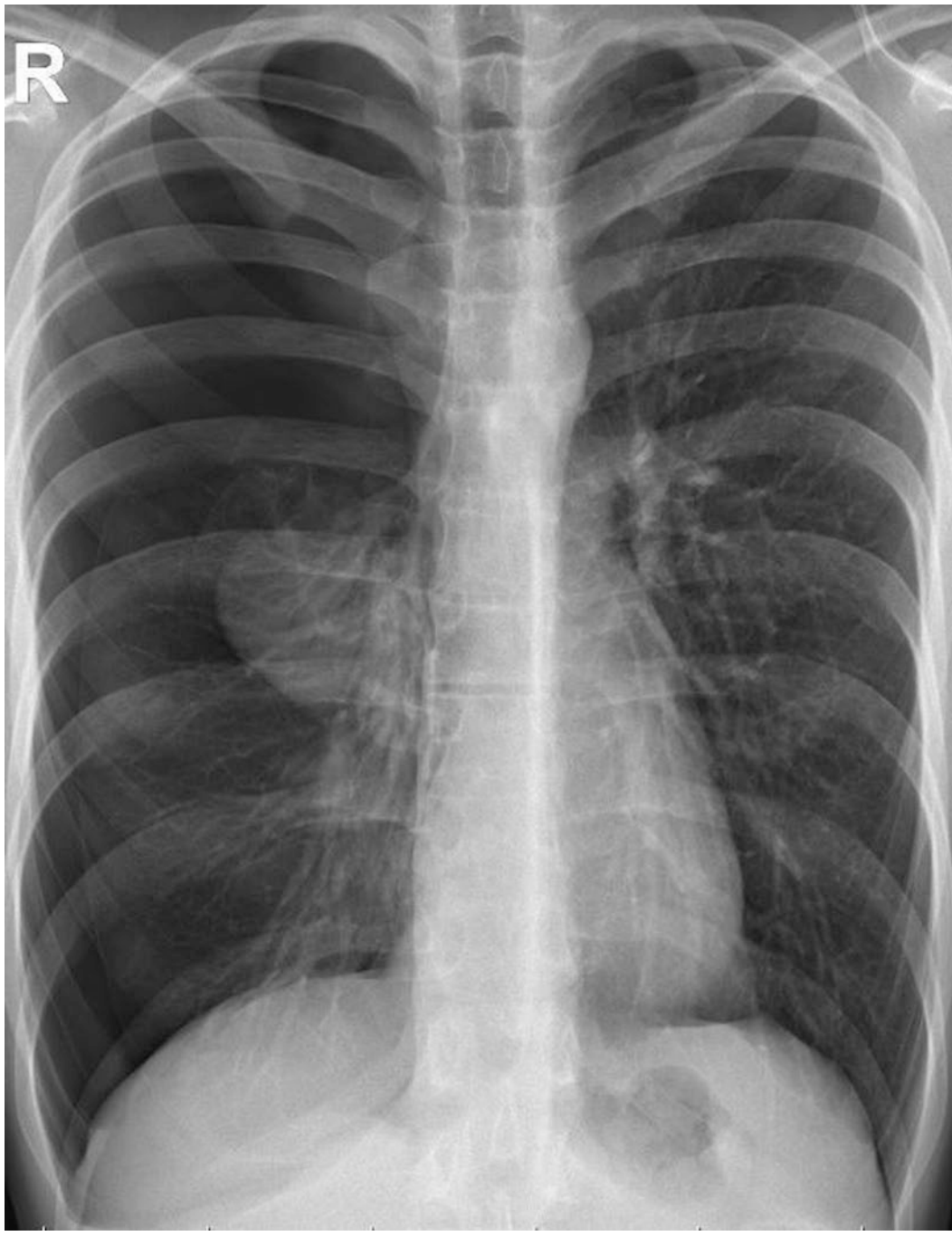

Fig. 2 Right pneumothorax after blunt chest trauma

traumas after a CT scan. It is considered the most common lesion in patients after severe blunt traumas, with a reported prevalence of 17–70% [6].

Patients may be asymptomatic or present with rapidly developing severe hypoxia and the need for mechanical ventilation.

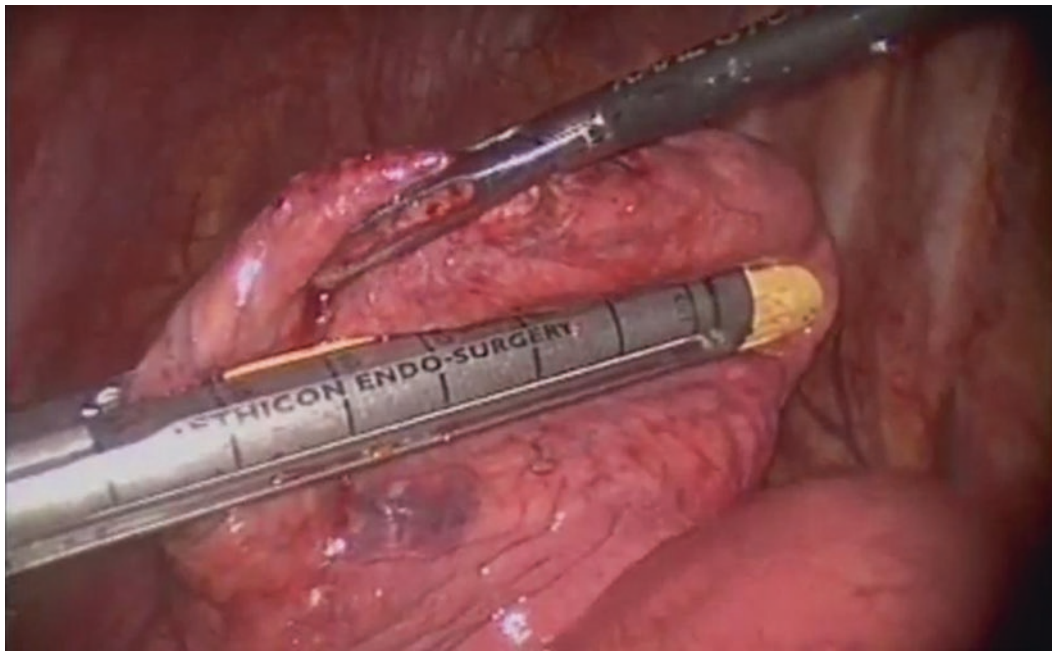

Fig. 3 Videothoracoscopic view of wedge resection of the right upper lobe for persistent air leak after simple pneumothorax in blunt chest trauma

Management of a pulmonary contusion is primarily supportive, and surgery is not needed if no other associated conditions require it.

Pulmonary Lacerations

A pulmonary laceration is defined as a disruption of the alveolar space with loss of the standard parenchymal structure. It occurs as a consequence of disruption and tearing of the lung parenchyma following shearing forces (Fig. 4). There are four types of lung lacerations [7]:

1. Compression rupture injury (the most common type): central lesions that may enlarge and compress the lung against the tracheobronchial tree
2. Compression shear injury: secondary to sudden squeeze of the lower lobes against the spine
3. Rib penetration tear: peripheral lesions, frequently associated with pneumothorax
4. Adhesion tear: adjacent to a previous pleuropulmonary adhesion

Small parenchymal lacerations may be filled with air (pneumatocele), blood (haematoma) or both (haematopneumatocele), are usually clinically insignificant and tend to resolve spontaneously. There may be a solitary lesion or multiples ones, creating a "Swiss cheese appearance". Uncommonly, small lacerations may become infected. Thus, antibiotics, postural drainage, and/or percutaneous drainage are indicated.

If the laceration involves the visceral pleural, pneumothorax is usually the primary problem, while the haemorrhage may cease thanks to the low blood pressure of the pulmonary circulation. In these patients, chest tube insertion is the most common treatment and often the only one needed. In fact, in 85% of patients after blunt traumas, the only treatment is observation or chest tube insertion. Only a low percentage of patients requires an Emergency Thoracotomy, defined as a thoracotomy within 24 hours of

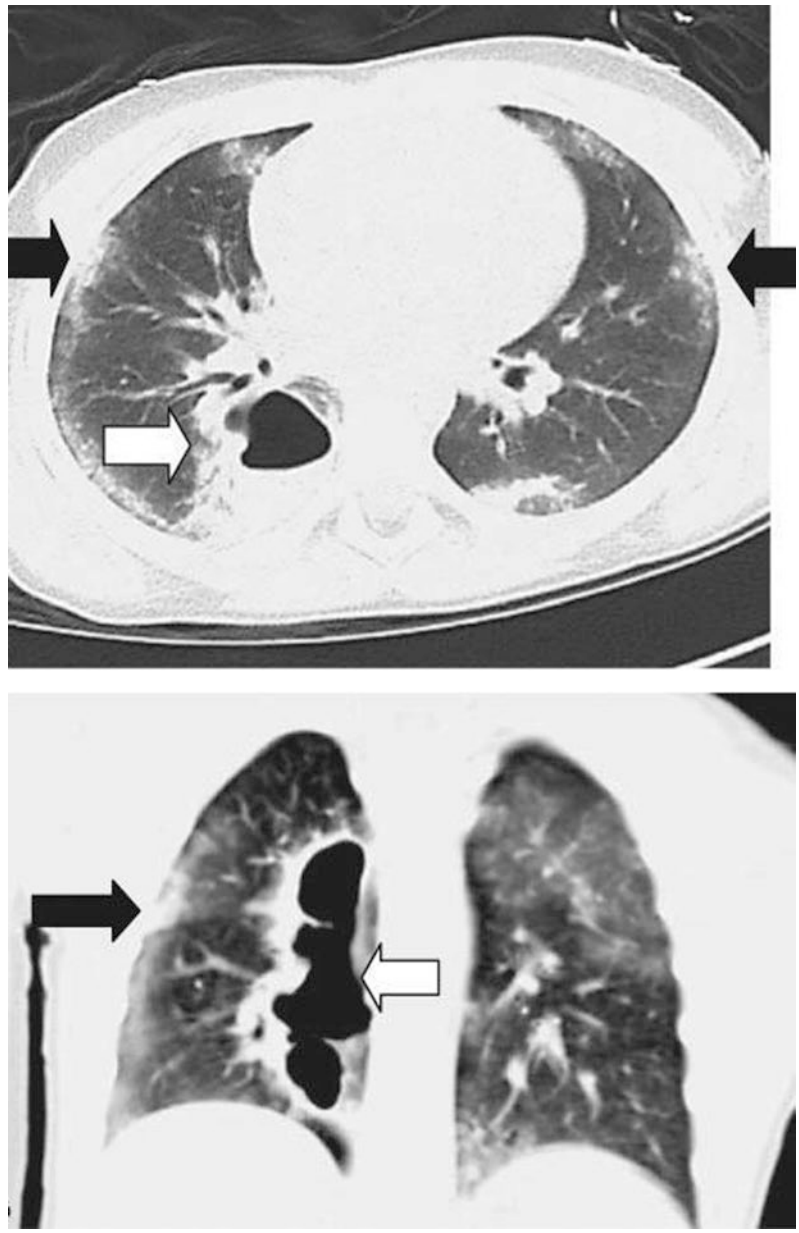

Fig. 4 Pulmonary laceration of the right lung (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2834257/figure/F1/)

trauma. Large lacerations after severe blunt traumas may be life-threatening conditions.

When surgery is mandatory, the use of non-anatomic and lung-sparing techniques has been advocated as the mortality increases correlates with the extent of the lung resection [8]. The emergency approach in these patients is usually open surgery, either with anterolateral or posterolateral thoracotomies (even though in rare cases a transverse sternotomy is necessary to provide adequate exposure), but video-assisted thoracic surgery is gaining importance. The most common procedure required is elimination of potential bleeding or air leaks by simple suture repair or wedge resection. Otherwise, the management of grave lobar injuries is more

controversial. Tractotomy is usually used to deal with peripheral transfixation or grave injuries. It consists of opening the laceration tract by firing a mechanical stapler and exposing the bleeding vessels to allow ultimate control of them (Fig. 5). Rarely, when extensive lung maceration is present or both arteries and veins are injured, the only opportunity is to fire a liner stapler across the hilum, the procedure defined as "simultaneous stapled pneumonectomy". However, this kind of procedure should be avoided whenever possible since it carries a mortality rate between 50 and 100%, keeping the debate open about its usefulness.

Tracheobronchial Injuries

Tracheobronchial injury is a rare but potentially fatal condition, often associated with injuries to adjacent structures. Nowadays, iatrogenic injuries are the most common ones, followed by blunt and finally penetrating ones.

Blunt tracheobronchial traumas have a mortality rate of up to 80% within one hour of injury, with an incidence of 0.5% in polytraumatized patients admitted to intensive care units [9].

Site of the lesion may be the cervical trachea or the intrathoracic tracheobronchial tree. In blunt traumas, most of the injuries occur within 2.5 cm of the carina, secondary to a sudden deceleration resulting from a motor vehicle accident or a fall.

Early diagnosis is mandatory to prevent significant complications, but it may be difficult, especially if typical signs and symptoms such as subcutaneous emphysema, difficulty speaking, respiratory distress, pneumothorax or haemoptysis are delayed. Clinical scenario and chest X-rays, showing pneumomediastinum, pneumothorax and subcutaneous emphysema, suggest the diagnosis that is confirmed by bronchoscopy, which is particularly useful to identify the location of the lesion and to help intubation beyond it.

Treatment is expectant or operative, depending on the nature and severity of the injury. A conservative approach may be chosen in case of stable subcutaneous emphysema, stable pneumomediastinum, spontaneous ventilation, absence of pneumothorax or air-leaks, and absence of mediastinitis. Otherwise, in clinically stable patients with lesions longer than 4 cm, surgery is suggested. Surgical approaches include thoracotomy, sternotomy, clamshell incision, cervical incision and different strategies to repair the lesion. All of them aiming at avoiding an unnecessary dissection of the airway that jeopardises the vascularity of the trachea and risking damage the recurrent laryngeal nerves. The cervical and upper two-thirds of the thoracic trachea are accessible through a cervical collar incision; the Angelillo-Mackinlay technique or a combined transcervical-transtracheal approach may be used to repair the tears (Fig. 6) [10, 11]. A partial sternotomy is seldom required.

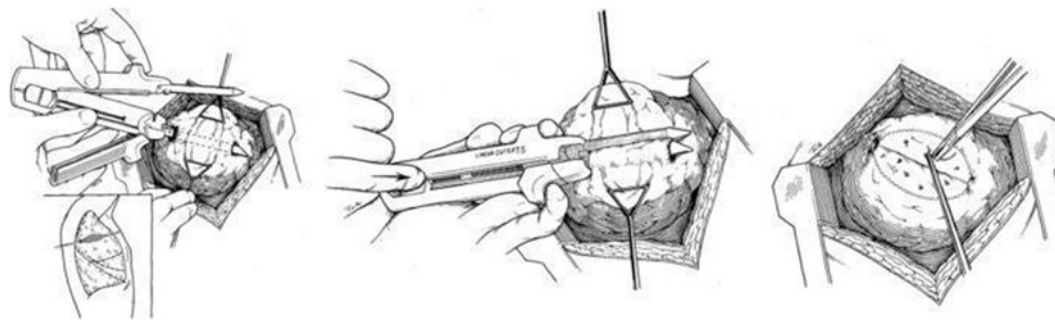

Fig. 5 Tractotomy using a mechanical stapler (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5628971/figure/f3-kjtcv-50-399/)

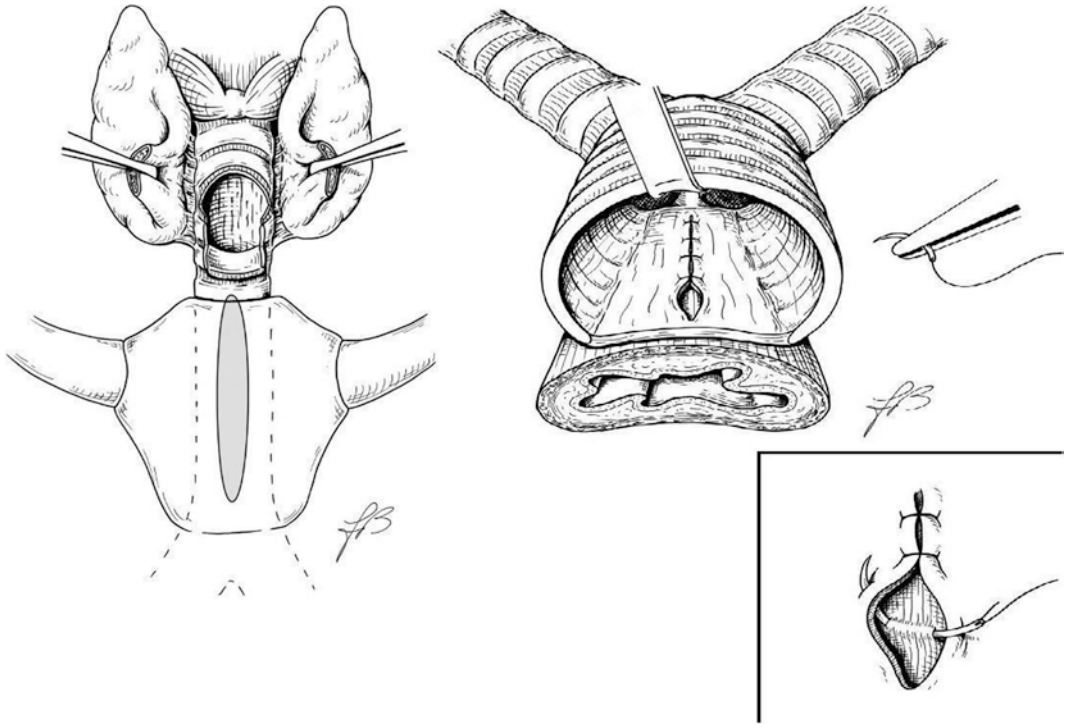

Fig. 6 Transcervical transtracheal repair of a tracheal tear (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2640036/figure/F1/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2640036/figure/F3/)

Tears in the lower third of the trachea, carina or right main bronchus are usually best approached through a right thoracotomy. Injuries of the left main bronchus are approached through a left thoracotomy.

All suture lines should be covered with well-vascularized tissue flaps and tested for air leaks.

Chest Wall Injuries

Blunt chest traumas may cause injury to every bone of the thorax. Scapular and clavicular fractures may be shared, but rarely require surgery. The ribs are the most commonly injured component of the thoracic cage, occurring in about 10% of chest traumas and 20% of severe injuries; they are often associated with other injuries and determine significant morbidity for their subsequent complications. Flail chest occurs when at least three ribs are fractured in two or more points, creating a part of the chest wall that moves independently with respiration. Sternal fractures are common after motor vehicle accidents secondary to direct impact of the anterior chest against steering wheels or the dashboard; considering the force needed to damage the sternum, it is not difficult to understand that sternal fractures are associated with an increased incidence of both, cardiac and significant vessel injury.

The following paragraphs focus on the treatment of chest wall injuries; see chapter "Lung Retransplantation" for general aspects of chest wall traumas.

Rib Fractures and Flail Chest

The management of rib fractures may vary widely from observation and bed rest to major surgery. The treatment approach strongly depends on which ribs and how many of them are injured.

In the case of simple rib fractures, the primary goal is optimal pain control to facilitate adequate pulmonary hygiene and avoid secondary complications. Pain relief is essential to enable adequate ventilation, and it can be obtained with oral or systemic analgesics, intercostal nerve block, or epidural anaesthesia. Each of these modalities has advantages and disadvantages that have to be taken into consideration in each patient. Surgery is limited to a small number of patients with severe pain due to fracture non-union or deformity.

Flail chest has been studied extensively; thus, its treatment has changed over the years. Management is, once again, directed to aggressive pain control and pulmonary toilet, trying to avoid mechanical ventilation unless it is strictly necessary. Anyhow, surgery may be required to stabilise the chest wall adequately in order to restore the mechanics of breathing, preserve lung function and to reduce deformity and severe pain. It is contraindicated in hemodynamically unstable patients, septic patients, or when more life-threatening conditions are present.

There are a few basic principles involved in the surgical approach for chest wall stabilisation. The position of the patient depends on the type of flail chest (anterior, lateral or posterior). The incision should be curvilinear and just above the fractured ribs. Whenever possible, a muscle sparing incision should be used. The periosteum should be left intact in order to preserve blood supply to the bone and prevent postoperative pain. The fractures should be reduced and the broken rib segments re-approximated. Fixation should be obtained with the available tools (pericostal sutures, titanium plates, wires, Judet staple, etc.).

Although, in the last decade, more studies have been focusing on surgical fixation, showing that early fixation may reduce the late morbidities of flail chest, in terms of chronic pain and decreased lung function, further randomised clinical trials are warranted to determine the best treatment strategy.

Sternal Fractures

Sternal fractures are most often transverse and occur at the junction of the manubrium and the sternal body. Treatment is primarily supportive, similar to that for rib fractures, consisting of optimal pain control and proper pulmonary hygiene. Multiple fractures with overlapping fragments may require surgery with reduction, debridement, and fixation. Fixation may be done using a wide variety of wiring techniques (single peristernal or transsternal to figure-of-eight peristernal or pericostal sutures), or sternal plating, internal screws, or thermoreactive clips (Fig. 7). Once again, the choice depends on the available tools in each centre and the surgeon's experience with their use.

Diaphragmatic Injuries

The first description of a diaphragmatic injury after a trauma dates back to 1541; nevertheless, we still have difficulties in its diagnosis because history and physical examination lack sensitivity and specificity and radiological evaluation may be negative at the beginning. Blunt diaphragmatic injuries incidence is 0.8–1.6% in blunt trauma patients admitted to hospital [12], and they are often associated with damage to other organs. See chapter "Lung Retransplantation" for General Aspects of Diaphragmatic Injuries.

From a surgical point of view, diaphragmatic lesions can be divided into two main groups: acute injuries and chronic traumatic diaphragmatic hernias. Both injuries are graded according to the American Association for the Surgery of Trauma (AAST) Organ Injury Scale for Diaphragmatic Injuries (Table 1) [13]. Nevertheless, all diaphragmatic injuries should be repaired, either with a direct suture or, less frequently, with a prosthetic mesh, for the risk of complications such as incarceration, possible strangulation and pulmonary compression is high.

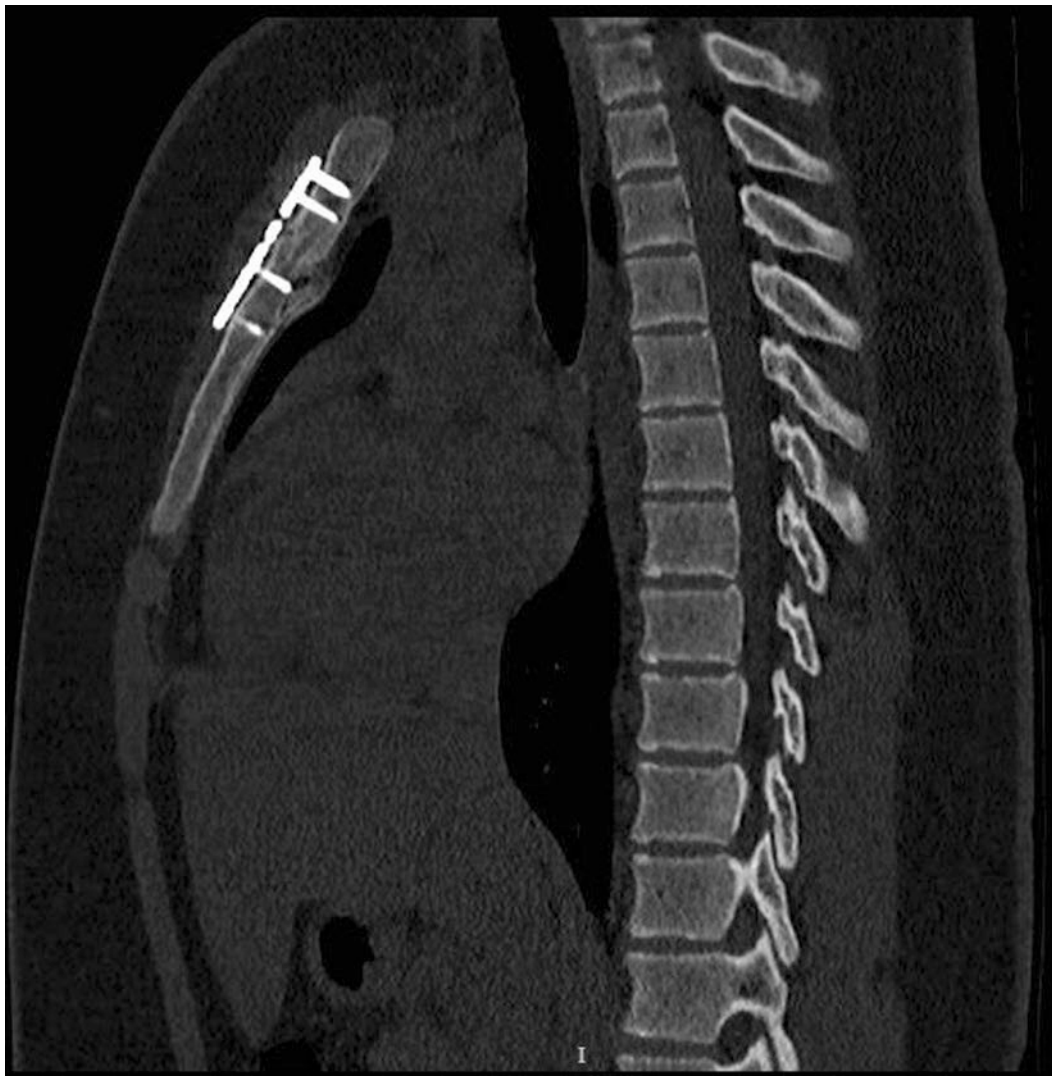

Fig. 7 Chest CT scan showing sternal fracture stabilized with titanium bars and screws

Table 1 AATS grade of diaphragmatic injuries

Grade	Injury
I	Contusion
II	Laceration $\leq$2 cm
III	Laceration 2–10 cm
IV	Laceration >10 cm with tissue loss $\leq$25 cm^2
V	Laceration with tissue loss >25 cm^2

There are two principles to follow in repairing acute diaphragmatic hernias:

- Reduction of the herniated organs back into the abdomen
- 'Watertight' closure of the hernia in order to prevent recurrence

The surgical options include minimally invasive surgery (laparoscopy or thoracoscopy) or open surgery (laparotomy or thoracotomy). Generally, an abdominal approach is suggested in cases of acute herniation secondary to abdominal trauma; on the contrary, a transthoracic surgery is recommended in delayed rupture. Anyhow, the type of approach should be customised for each patient, taking into consideration eventually associated injuries and the approach needed to deal with them or stop a source of bleeding.

From the abdomen, the right hemidiaphragm is inspected after transection of the falciform ligament and downward traction of the liver, while the left hemidiaphragm can be exposed by applying gentle downward traction of the spleen and greater curvature of the stomach. Reduction of the herniated organs is usually straightforward in the acute phase when no adhesions are present. After debridement of the edges of the laceration, these are grasped to inspect the pleural cavity to look for any bleeding or other injuries and then approximated. It is suggested to repair defects using interrupted number #0 or #1 non-absorbable braided sutures; anyhow there are different methods, such as interrupted figure of eight or horizontal mattress sutures, running hemostatic suture lines, a double layer repair etc. (Fig. 8). Once repaired, the line of the suture should be tested with the field flooded with sterile saline. The use of prosthetic material for diaphragmatic reconstruction in the acute setting is rarely needed.

Repair of chronic diaphragmatic hernias should be performed electively, unless in case of visceral obstruction, strangulation or incarceration, when urgent surgery is indicated. They can be repaired either transabdominally or transthoracically (open or minimally invasive surgery); the choice of the approach again depends

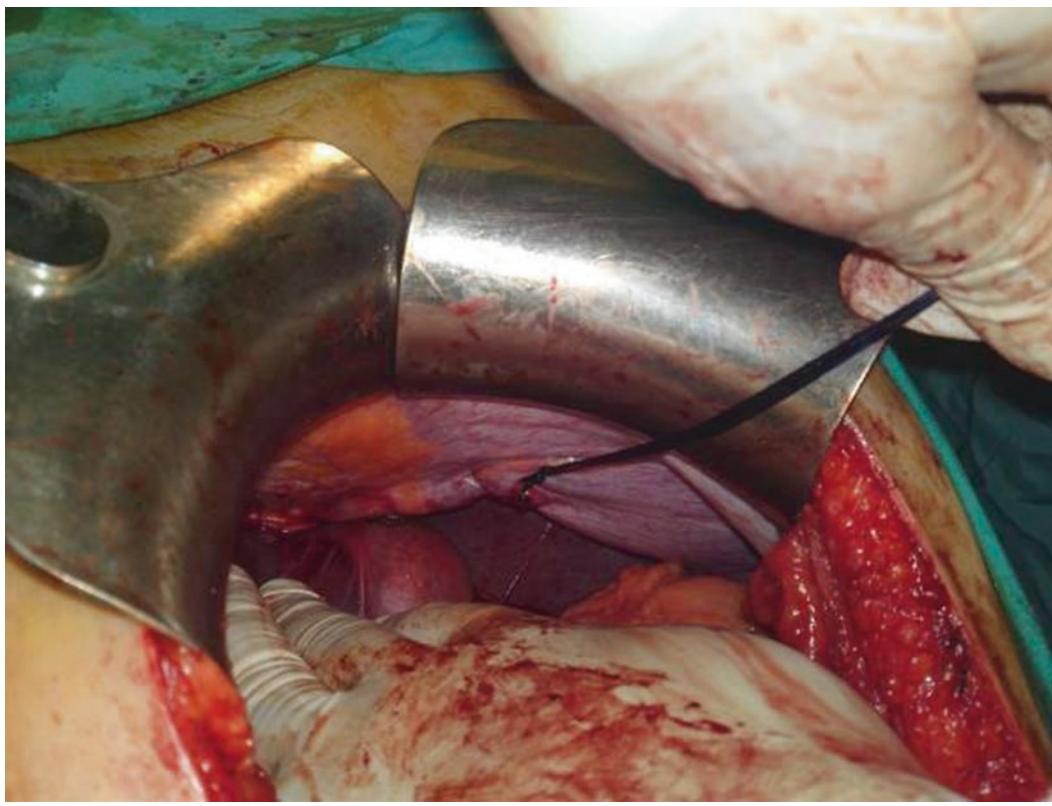

Fig. 8 Transabdominal repair of a diaphragmatic injury (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3423012/figure/F4/)

on the surgeon's subspecialty. The transthoracic approach offers several benefits: the lysis under direct vision of intrathoracic adhesions, decortication if needed, avoidance of abdominal adhesions from previous surgery. A posterolateral thoracotomy at the sixth or seventh intercostal space is the most common incision in case of open surgery; video-assisted thoracoscopic surgery may be performed with one, two, three or more accesses according to the surgeon's preference and abilities. No matter which approach is used, once all organs are repositioned into the abdomen, the diaphragm is repaired using the same principles described as for acute injuries. Occasionally, significant defects (>8 cm) may require the use of synthetic patches; the most common ones include polytetrafluoroethylene (PTFE), polypropylene, and polyester. Generally, once the mesh is tailored according to the diaphragm hernia, it is fixed to the edges of the defect using interrupted number #0 or #1 non-absorbable braided sutures. Rarely, it may be necessary to secure the mesh to the ribs. In children or contaminated fields, autologous tissue may be used; the most commonly utilised autologous tissues are pedicled latissimus dorsi and serratus anterior muscle flaps. Once the defect is closed, the sealing of the suture must be tested.

The prognosis following a blunt injury to the diaphragm depends on the associated injuries (acute phase) or the presence of bowel ischemia, necrosis and sepsis (chronic phase).

Oesophageal Injuries

Oesophageal injuries, while uncommon, have severe consequences with high morbidity and mortality. Nowadays, most of these injuries are iatrogenic; the second most common injuries are due to penetrating trauma. Blunt traumas to the oesophagus are rare and secondary to motor vehicle accidents. The high energy required to injure the oesophagus bluntly often results in multiple-organ injuries.

Diagnosis may be difficult due to the rarity of these injuries, the scarcity of initial clinical signs, and the associated injuries that delay its recognition. The clinical presentation depends on the site of injury and the time of its identification. Dyspnoea, cyanosis, subcutaneous emphysema, pneumomediastinum, sepsis, and shock may be present.

Early diagnosis is essential for the patient. Chest X-ray and endoscopy direct the clinician. Contrast swallow is an alternative diagnostic option when endoscopy is not available. In general, a water-soluble agent should be used as a first-line contrast, although it is less sensitive than barium (50% of perforations of the cervical oesophagus vs. 60% with barium and 80% of the thoracic oesophagus vs. 90% with barium), since the latter can lead to mediastinitis if leaking outside of the esophagus. In intubated patients, the contrast can be instilled via a nasogastric tube that is pulled back to the proximal esophagus. Contrast studies may miss esophageal injuries, but when combined with flexible esophagoscopy, the diagnosis of esophageal injuries may be obtained in virtually every patient. Endoscopy is a useful tool also for the treatment of critically ill patients and/or those who suffer from multiple other injuries. Various intraluminal stents can be used to deal with perforations; it should cover the entire length of the tear, and have a safe margin of a few centimeters above and below the injury. However, some perforations are not suitable for stenting, such as high cervical injuries or tears at the esophagogastric junction; in selected cases, clipping may be useful. While endoscopy may be effective at controlling the leak, it does not control any extraluminal contamination, so appropriate drainage or even surgery is sometimes mandatory to address this issue.

Immediate surgery with primary repair and adequate tissue buttressing is mandatory.

Management of oesophageal traumas, despite the aetiology, should follow some basic principles:

- Control of contamination and drainage of contaminated areas, abscesses and fistulas
- Repair or exclusion of the tear

– Restoration of the continuity of the gastrointestinal tract
– Nutritional support

Surgery is indicated when the patient is stabilised. However, the repair should be done as soon as possible -the earlier the intervention, the better usually the overall prognosis.

Surgery has different variables, depending on:

- the location of the injury
- the extent of the injury
- the time of diagnosis and contamination
- any associated lesions
  – injury to other structures
  – fistula
  – pre-existing diseases

There are different options for the management of esophageal injuries, including a conservative approach with the insertion of a nasogastric tube and antibiotics, primary repair, T-tube drainage, exclusion and cervical stoma, esophagectomy and stomach or colon pull-up.

The conservative approach is the primary treatment of small, self-limited lesions.

A T-tube with extensive drainage is limited to critically ill patients or delayed diagnosed lesions.

In gross contamination or extensive destruction of the oesophagus, oesophageal exclusion and cervical stoma may be indicated, with the restoration of the continuity of the gastrointestinal tract in a second moment.

Esophagectomy and stomach or colon pull up may be indicated in stable patients, with underlying disease (distal stenosis or occult oesophageal cancer), without mediastinitis or as an emergency “salvage” surgery.

Anyhow, the primary goal is a direct repair of the lesion, maintaining the normal anatomy of the upper gastrointestinal tract.

Cervical oesophageal injuries are reached through left lateral cervicotomy along the sternocleidomastoid muscle. The mid-thoracic oesophagus is better approached through a right posterolateral thoracotomy at the IV-V-VI intercostal space, whereas the distal oesophagus through a left posterolateral thoracotomy at the VII-VIII intercostal space. The oesophago-gastric junction is reached preferentially through a laparotomy.

The principles and techniques used to manage primary repair are similar in every region. Devitalized nearby tissues and oesophageal tissues should be debrided. It is essential to keep in mind that the defect in the muscular layer is almost always less extensive than the one in the mucosa. Oesophageal repair is usually performed using two layers of interrupted number 3-0 absorbable sutures, one for the mucosa and one for the muscular wall; also, full-thickness sutures are a suitable alternative method.

The suture line should always be reinforced with a flap; depending on the location, the chosen flap can be a strap, sternocleidomastoid or the pectoralis major muscle (cervical tears); an intercostal muscle, pleura, pericardium, diaphragm or mediastinal fatty tissue (intrathoracic tears); omentum or fundal wrap (abdominal tears). Finally, extensive drainage of the region is mandatory.

Oesophageal injuries consist of a wide variety of problems to deal with and are associated with high mortality rates (~10%) and no accepted guidelines yet; there is no consensus on the type and timing of the repair. Most of the recommendations come in the form of retrospective analyses from major centres. Thus, further studies are needed to define the best management for these patients.

Conclusions

Blunt thoracic traumas include a wide variety of diseases and injuries; they are often associated with multi-organ lesions that increase the mortality exponentially. Their management requires quick and accurate decision-making, made possible by basic and advanced knowledge. The purpose of this chapter is to help in the choice of the path to follow to optimally patients with blunt chest traumas.

Exercises/Self-study

1. Which of the following are complications of retained hemothorax?
   a. empyema
   b. fibrothorax
   c. loss of pulmonary function
   d. a b and c
2. When is a conservative treatment in patients with tracheobronchial injuries contraindicated?
   a. stable pneumomediastinum
   b. spontaneous ventilation
   c. increasing subcutaneous emphysema
   d. absence of pneumothorax or air-leaks
3. Which statement about diaphragmatic injuries is correct?
   a. defects <8 cm are always corrected with prosthetic mesh
   b. in case of acute diagnosis, surgery is never indicated
   c. in case of late diagnosis, the transthoracic approach is the most commonly recommended technique
   d. repair with interrupted sutures is rarely indicated
4. The best approach in a patient with a mid-thoracic injury of the oesophagus is:
   a. cervicotomy
   b. right thoracotomy
   c. left thoracotomy
   d. thoracoabdominal access
5. Which is the most common treatment in uncomplicated pulmonary lacerations:
   a. conservative approach
   b. emergency thoracotomy
   c. lobectomy
   d. sleeve resections

Answers

1. Which of the following are complications of retained hemothorax?
   a. empyema
   b. fibrothorax
   c. loss of pulmonary function
   d. a b and c

   CORRECT: D. all the aforementioned are complications of a retained hemothorax.
2. When is a conservative treatment in patients with tracheobronchial injuries contraindicated?
   a. stable pneumomediastinum
   b. spontaneous ventilation
   c. increasing subcutaneous emphysema
   d. absence of pneumothorax or air-leaks

   CORRECT: C. A conservative approach in tracheobronchial injuries (<4 cm) may be chosen in case of stable subcutaneous emphysema, stable pneumomediastinum, spontaneous ventilation, absence of pneumothorax or air-leaks, or absence of mediastinitis.
3. Which statement about diaphragmatic injuries is correct?
   a. defects <8 cm are always corrected with prosthetic mesh
   b. in case of acute diagnosis, surgery is never indicated
   c. in case of late diagnosis, the transthoracic approach is the most commonly recommended technique
   d. repair with interrupted sutures is rarely indicated

   CORRECT: C. Generally, the abdominal approach is suggested in cases of acute herniation secondary to abdominal trauma; on the contrary, a transthoracic surgery is recommended in delayed rupture. All diaphragmatic injuries should be repaired, either with direct suture or, less frequently, with prosthetic mesh (>8 cm).
4. The best approach in a patient with a mid-thoracic injury of the oesophagus is:
   a. cervicotomy
   b. right thoracotomy
   c. left thoracotomy
   d. thoracoabdominal access

   CORRECT: B. Cervical oesophageal injuries are reached through left lateral cervicotomy, the mid-thoracic oesophagus through a right posterolateral thoracotomy, the distal oesophagus through a left basal posterolateral

thoracotomy, and the oesophagogastric junction through a laparotomy.

5. Which is the most common treatment in uncomplicated pulmonary lacerations:
   a. conservative approach
   b. emergency thoracotomy
   c. lobectomy
   d. sleeve resections

   CORRECT: A. In 85% of patients after blunt traumas with pulmonary lacerations, the only treatment is observation or chest tube insertion.

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Open Thoracic Trauma

Claudiu E. Nistor and Adrian Cristian Dobrica

Key Points

- It is very important for a surgeon faced with multiple thoracic wounds to approach each wound systematically
- The majority of patients with open chest trauma can safely be managed with tube thoracostomy
- Tube thoracostomy alone is adequate treatment for most simple lung parenchymal injuries.

Definitions

Thoracic trauma can be classified as (1) closed (blunt) (in 70% of cases) and (2) open (in 30% of cases). Furthermore, open thoracic trauma can be classified as non-penetrating injuries (limited to the chest wall) (Fig. 1), and penetrating injuries (passing the parietal pleura and entering the thoracic cavity). Between 6 and 70% of open thoracic trauma are stab wounds produced by knives, having a mortality of 2–13% [3].

Non-penetrating Open Thoracic Trauma

Stab injuries often cause only minor problems, due to the low impact energy, while shot wounds on the other hand can cause serious problems through the extensive local destruction they can cause. Treatment is surgical and consists in stabilization of the thoracic wall with restoration of the soft parts integrity [4].

In patients with extensive tissue damage (muscles and bones—ribs and sternum) due to non-penetrating thoracic trauma, adequate exploration and closure are the main surgical concerns (Figs. 2, 3, 4, 5, 6, 7, 8 and 9) [5].

Presently, in some parts of the world, a significant number of non-penetrating open traumas are caused by bear attacks. The resulting injuries pose problems concerning adequate surgical management with prevention of infection (Figs. 10, 11 and 12).

Penetrating Open Thoracic Trauma

These kind of trauma are usually seen in the form of stab wounds or gunshot injuries, but in our statistics we found other major causes

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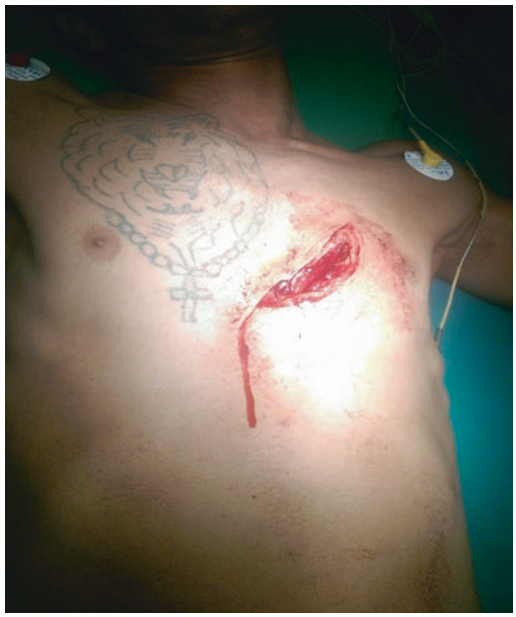


Fig. 1 Large left anterior stab wound limited to the chest wall

like: bear bites, domestic animal attacks (e.g. cow horns), work accidents (e.g. traumas caused by wood fragments, metal bars), and car accidents.

They are classified into three major groups [6]:

a. No exit wound—"sleeper" wounds.
b. Entrance wound and exit wound—perforating wounds,
c. Wounds in which the projectile penetrates through the whole intrathoracic cavity and remains in the subcutaneous tissue.

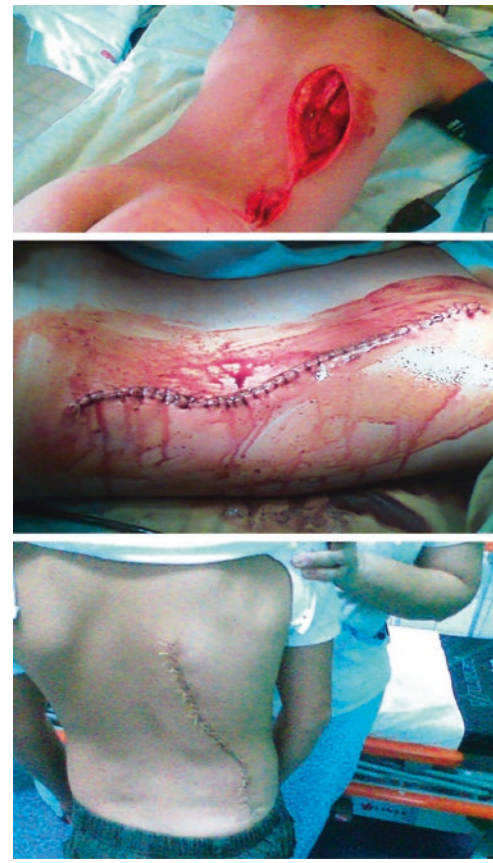


Fig. 2 Large posterior chest wall wound after accidental cutting by pool edge in an 11 year old boy, treated with primary layer-wise closure

About 15% of stab wounds and about 20% of gunshot wounds require thoracotomy [7]. The majority of patients with open chest trauma can safely be managed with tube thoracostomy [8].

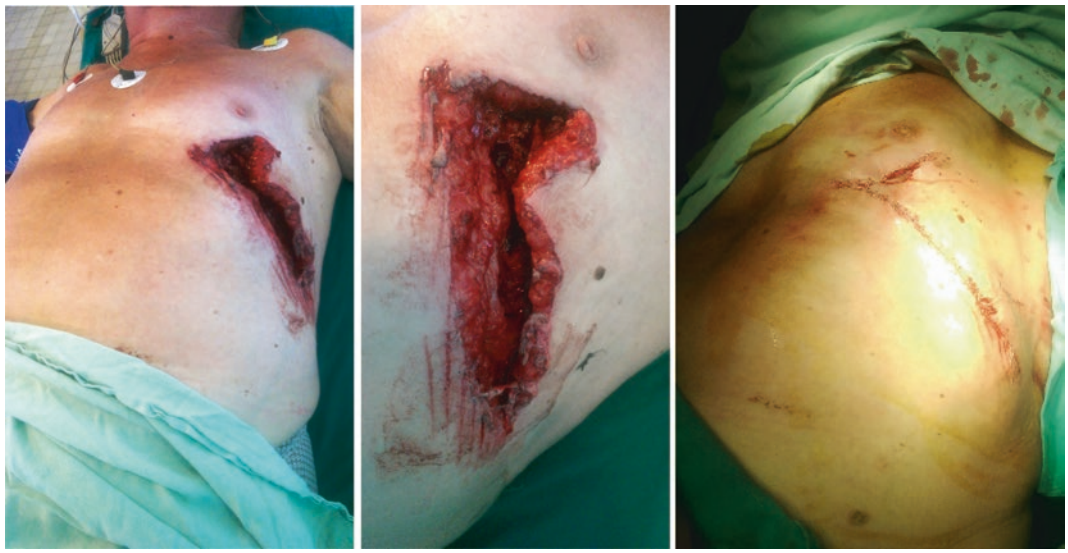


Fig. 3 Large anterolateral chest wall wound with extensive soft tissue and cartilage distruction after chainsaw accident in a 68 y.o. man, treated with extensive debridement and primary layer-wise closure

Indications for emergency thoracotomy are [4, 6]:

- Cardiac arrest or imminent cardiac arrest
- Evidence of cardiovascular injury, such as severe hypotension or severe active external or internal bleeding
- Immediate blood loss after tube thoracostomy of more than 1000–1200 ml
- Diagnosis of esophageal or tracheobronchial injury

It is very important for a surgeon faced with multiple thoracic wounds to approach each wound systematically [9].

Emergency Thoracotomy Approach (Clamshell Method)

- Intubate the patient, administer 100% oxygen and ventilate.
- Get 2x large-bore IV access, initiate massive transfusion protocol.
- Incise skin in the 5th intercostal space, starting from the costochrondral junction and continuing to the midaxillary line (the inframammary fold may be used as a guide).
- Divide the muscle, and parietal pleura. Internal thoracic arteries need to be ligated later as significant hemorrhage will occur as circulation is restored.
- Insert a rib-spreading retractor. Further distraction may be obtained by dividing the sixth rib posteriorly.
- To extend the incision to the right side cut through the sternum (using strong scissors, bone cutters or a Gigli saw) into the right fifth intercostal space.
- A Vertical pericardial incision is made anterior to the phrenic nerve in a bulging pericardium.

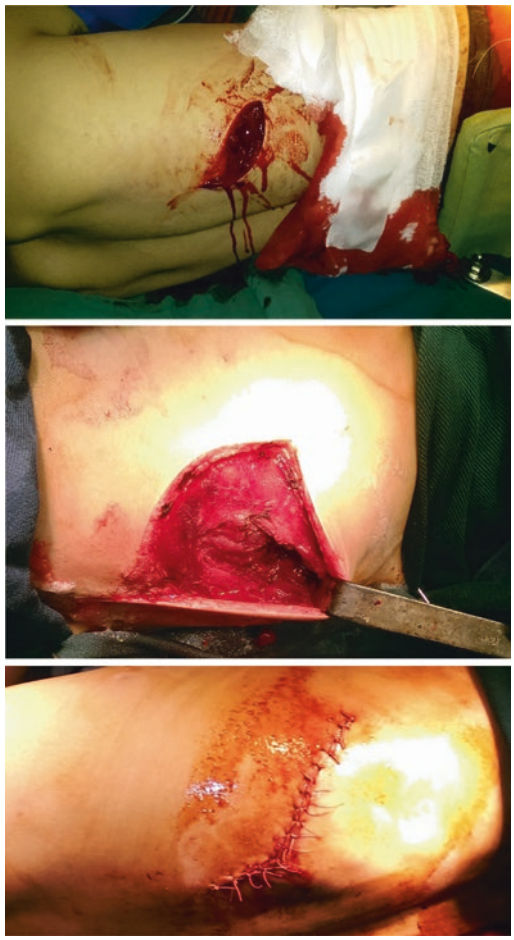


Fig. 4 Posterior large stab wound with muscle involvement, treated with layer-wise closure

- Place a finger over any cardiac defect. In a large cardiac defect we can place a sterile Foley catheter through the cardiac wound. Inflate the balloon, then apply gentle traction to close the hole and the fluid may be directly infused into the heart if other venous access is unavailable or keep the catheter clamped.
- Close myocardial defects (using buttressed Prolene sutures) avoiding the coronary arteries.
- In case of significant lung laceration with the risk of air embolism from bronchial-vascular communication, hilar clamping may be required.
- Internal cardiac massage compressing the heart between two flat hands.
- Defibrillate using small internal paddles either side of the heart with energy settings of 15–30 J (or biphasic equivalent).

Cardiac Injuries—Management (Figs. 13 and 14)

There are 2 main goals when approaching cardiac injuries in open thoracic trauma:

1. relieve pericardial tamponade,
2. control hemorrhage.

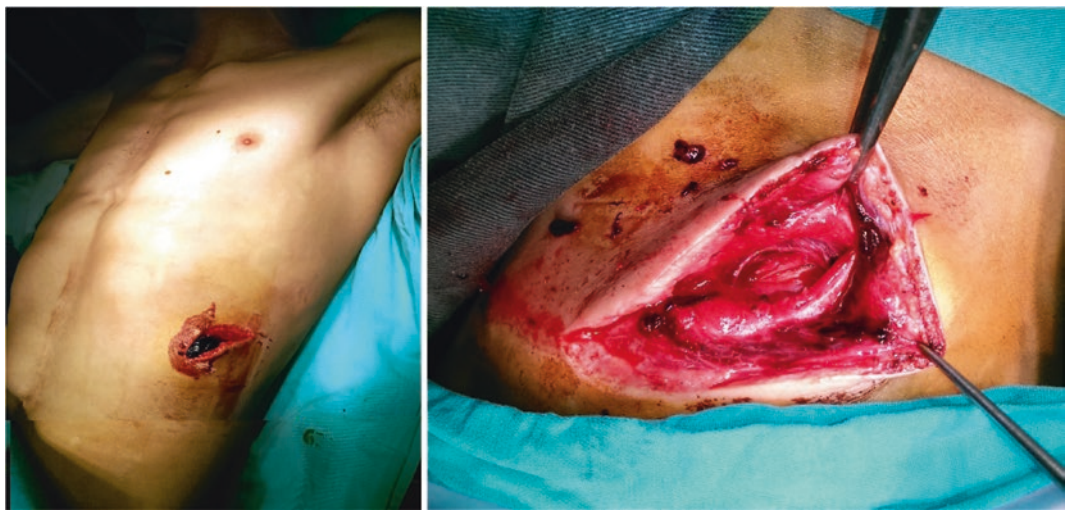


Fig. 5 Left anterolateral stab wound with cartilage lesion without entering the pleural space

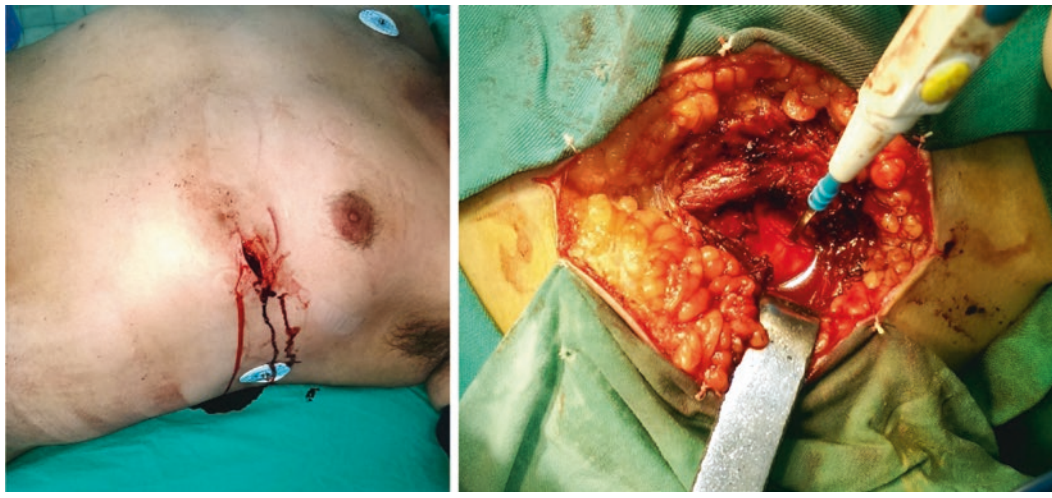


Fig. 6 Left anterolateral stab wound with longitudinal lesion of the 7th rib without entering the pleural space

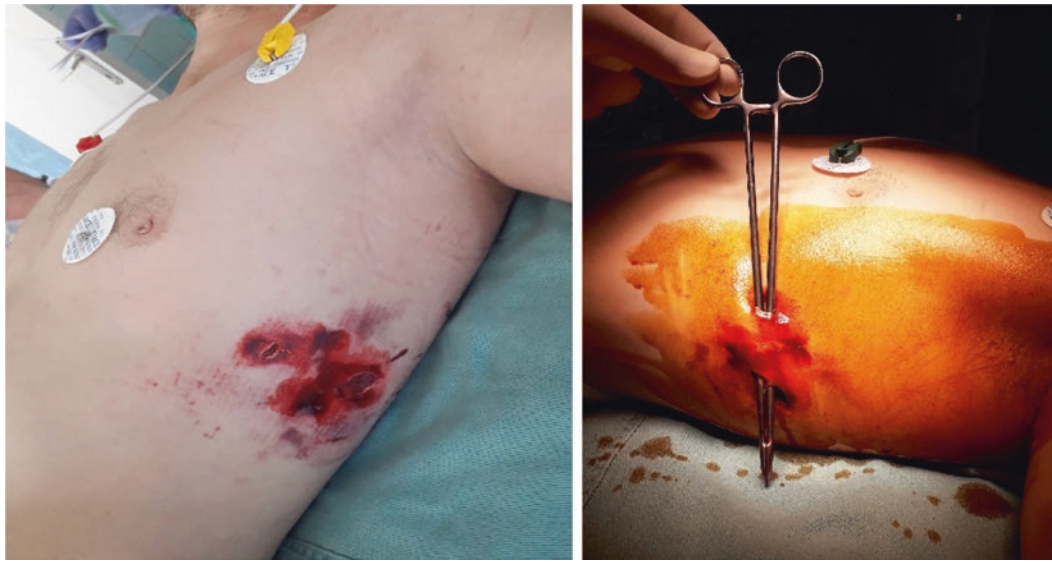


Fig. 7 Left basal ‚piercing through' wound of the soft tissues after car accident in a 34 y.o. man, associated with flail chest

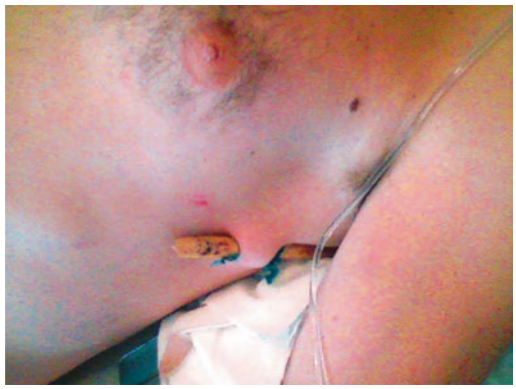


Fig. 8 Left ‚piercing through' wound of the soft tissues with retention of foreign body (fragment of wood and clothes) after work accident

Isolated wounds of the heart should be exposed by opening the pericardium and occluding the injury with finger pressure [4, 6]. Other methods are: the use of skin staples (particularly in large wounds or multiple injuries) or a Foley catheter (18 Fr). With the balloon inflated and traction applied to the catheter, Teflon-pledgeted sutures can then be passed from side to side of the ventricle over the balloon. Pushing the catheter and balloon into the ventricle with each bite of the suture will avoid the puncture of the inflated balloon in a case of a thin wall of the right ventricle, although blood loss may be significant.

In order to avoid cardiopulmonary bypass, in a case of a longitudinal perforation or significant rupture of a ventricle we can use the technique of inflow occlusion of the superior and inferior vena cavae with curved aortic or angled vascular clamps. Horizontal mattress sutures are then inserted rapidly on either side of the defect as the heartbeat slows and then crossed to control haemorrhage. Then, a continuous suture is

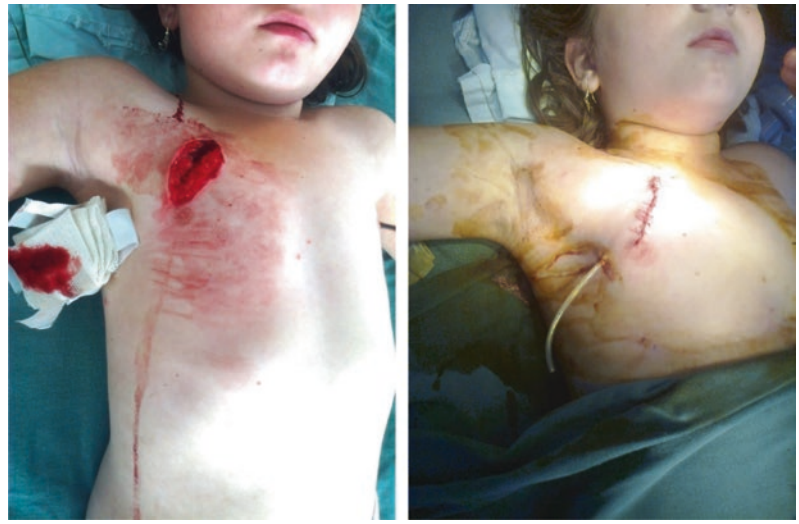


Fig. 9 Large right anterior soft tissue wound in a 9 y.o. girl after accidental cutting with a piece of glass

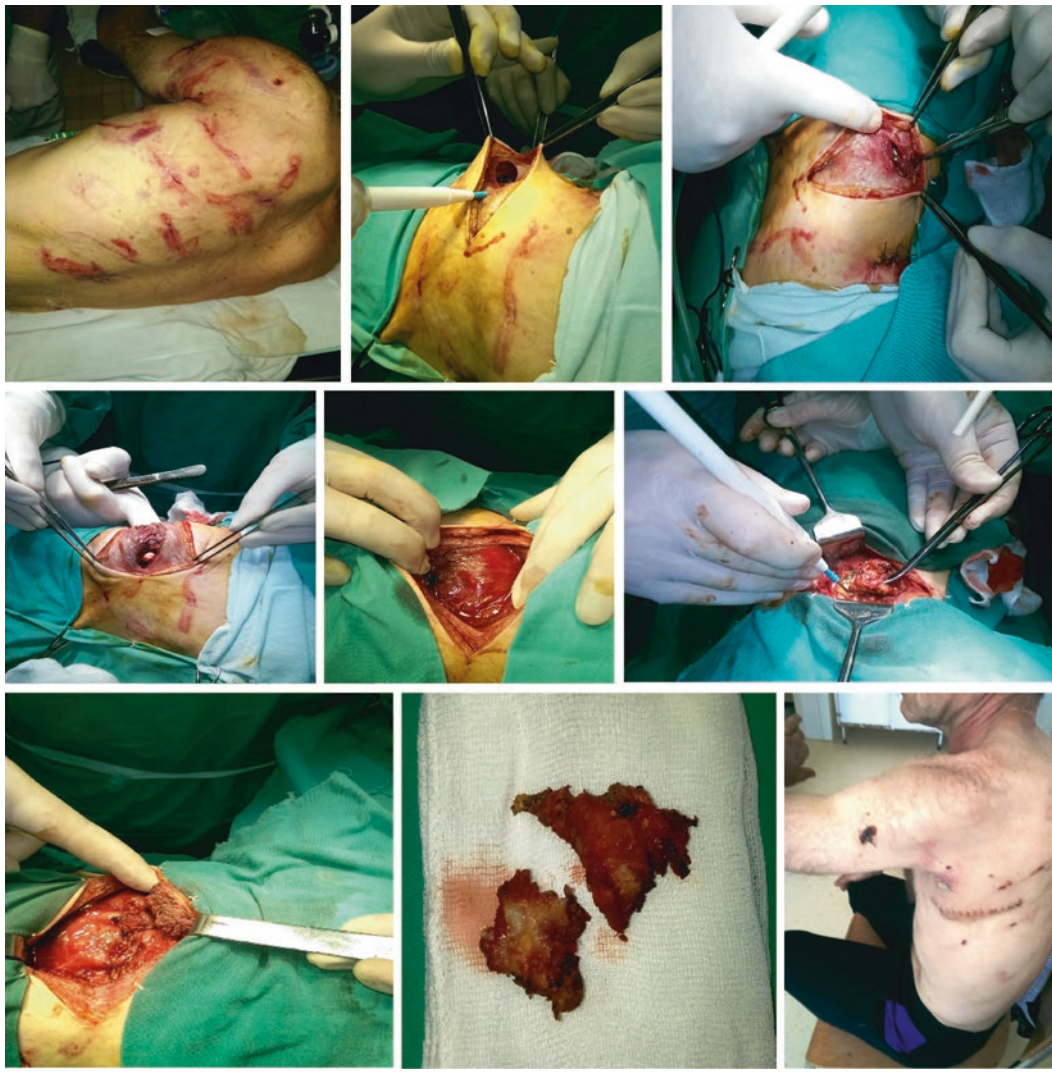


Fig. 10 Multiple bear bite wounds in a 48 y.o male, with muscle distruction and comminutive displaced fracture of left scapula, treated with excisional debridement (including detached scapula fragments), wound toilet and closure layer-by-layer

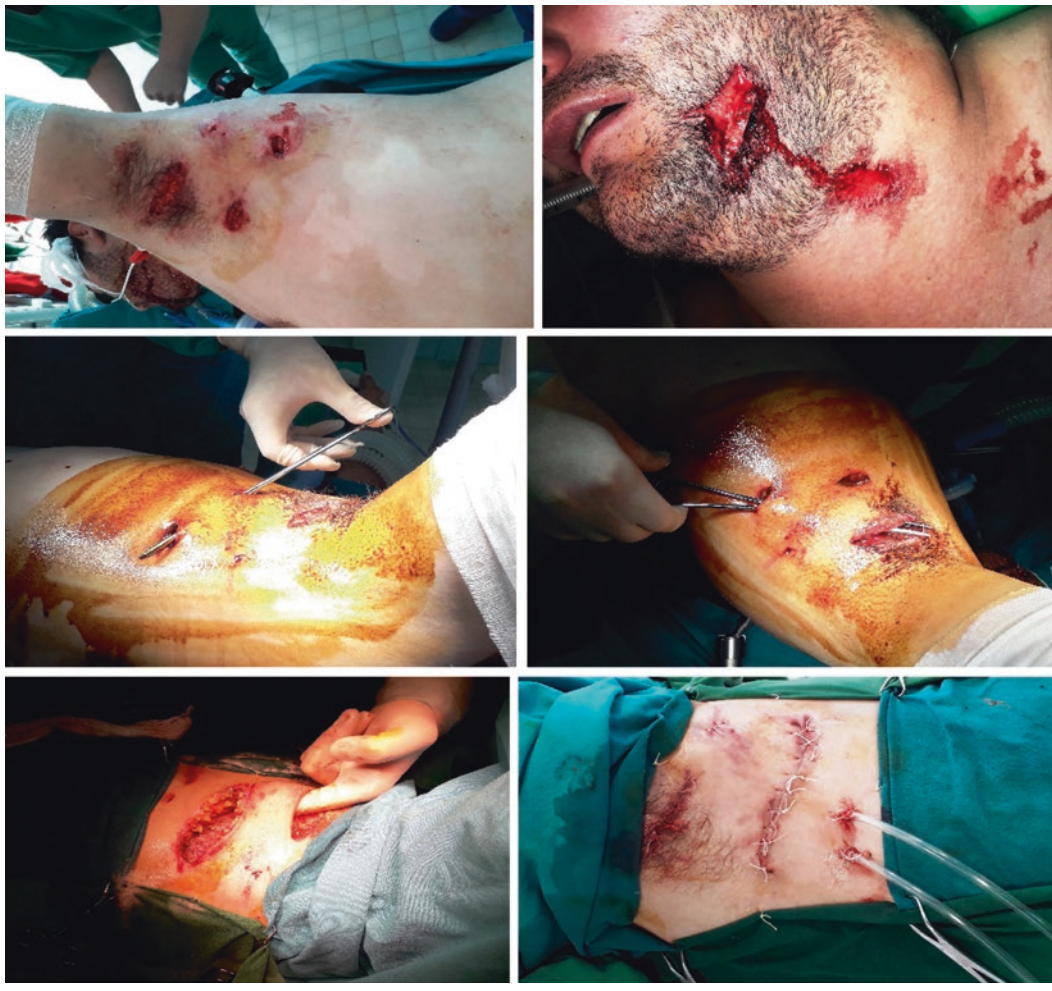


Fig. 11 Multiple bear bite wounds in a 26 y.o. male, with soft tissue distruction of left axilla an left lateral chest wall, treated with extensive debridement, toilet, drainage and skin closure

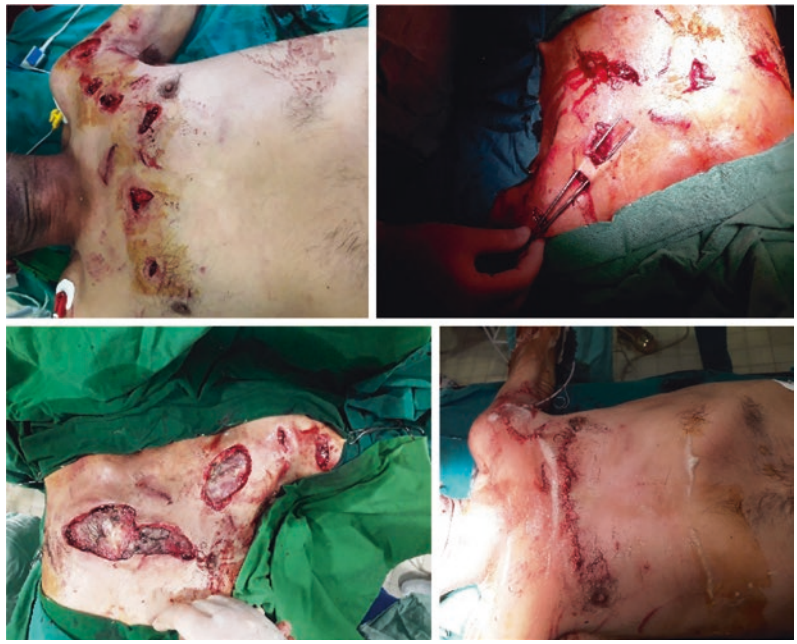


Fig. 12 Multiple bear bite wounds in a 47 y.o. male, with extensive soft tissue distruction of the anterior chest wall, treated by extensive surgical debridement, toilet and primary closure

placed to close the defect. Before it is tied down, air is vented out of the elevated ventricle by releasing the clamps on the cavae.

The pledgeted horizontal mattress sutures (2-0 or 3-0 Prolene) are used for definitive repair. Care must be taken to avoid injury of the coronary arteries. Atrial repairs may include: stapled repair, running suture closure or simple ligature [4, 6].

Pulmonary Injuries Management

Tube thoracostomy alone is an adequate treatment for most simple lung parenchymal injuries (Fig. 15) [8].

Large air leaks not responding to thoracostomy will require thoracotomy and open repair. Simple lung bleeding from superficial lacerations of lung parenchyma should be controlled

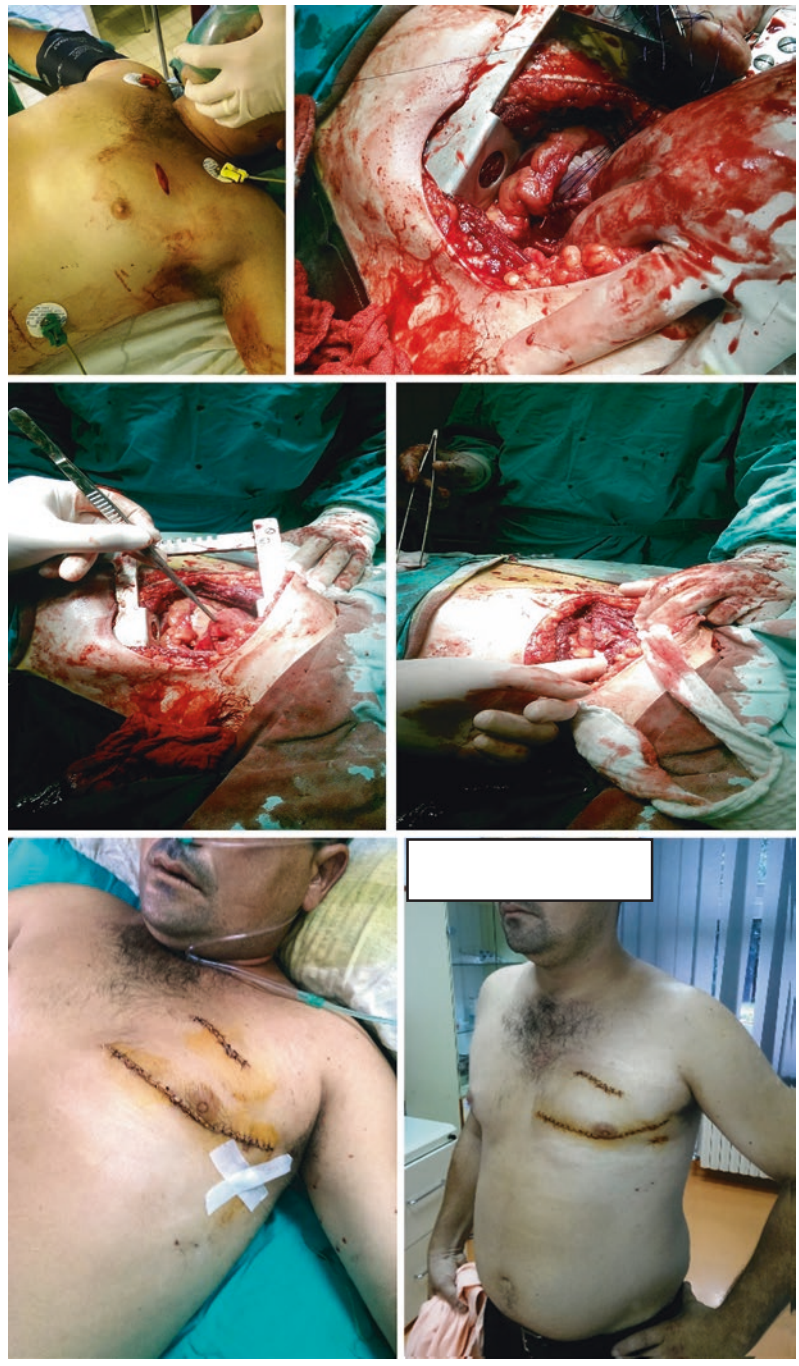


Fig. 13 35 y.o. male presenting with a penetrating stab wound, cutting the 4-th rib cartilage, injuring the ventral segment af the left upper lobe and producing a large (35 mm) wound in the left ventricle. At admittance: blood pressure 60/40 mmHg, SaO_2 91% (with O_2 administration), severe altered status. Through a left anterolateral thoracotomy we performed a large pericardotomy starting from the pericardium injury, finger pressure over the injury and suture of the ventricle wall with separate stitches using 3-0 prolene, followed by pulmonary suture. Postoperative outcome was uneventful, the patient being submitted to multiple echocardiographies during cardiac follow-up without pathologic findings

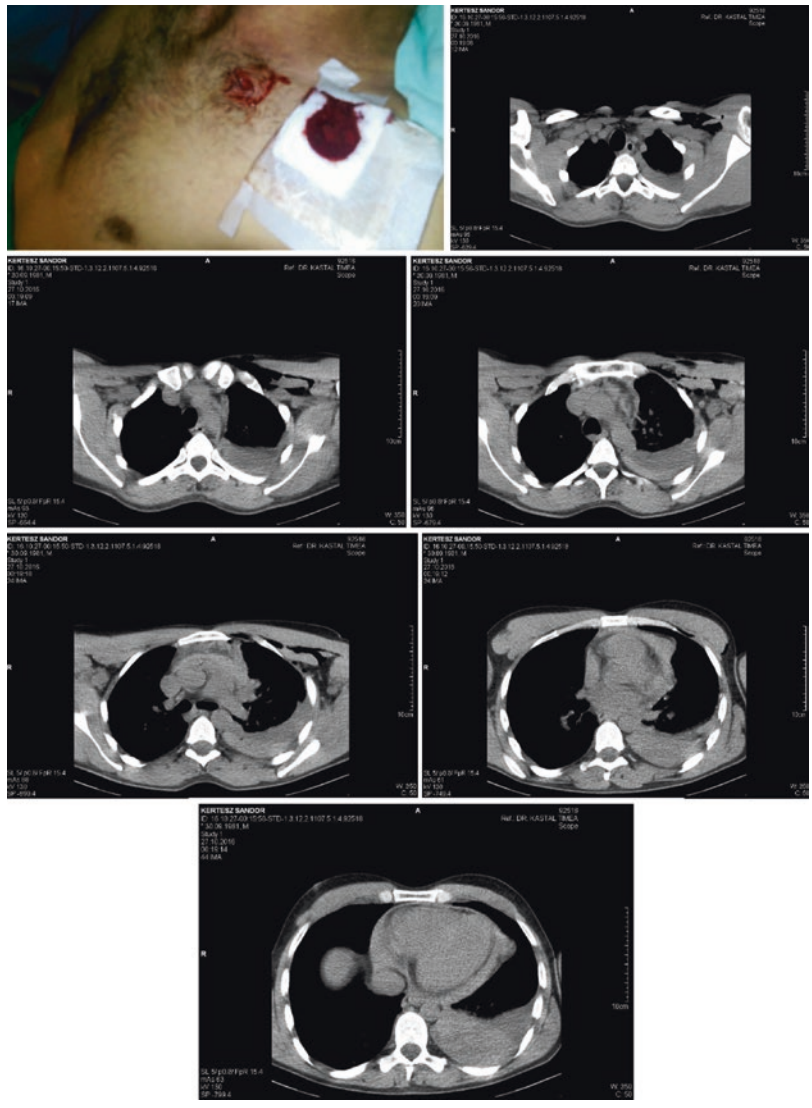


Fig. 14 35 y.o. male presenting with a penetrating stab wound, entering thorax through 2nd intercostal space in the left midclavicular line. The CT scan shows left pneumothorax and a large amount of fluid (blood) inside the pleural cavity and pericardium associated with a posterior mediastinal hematoma. We performed a left posterolateral thoracotomy, finding approximately 1200 ml of fresh blood in the pleural cavity from a 20 mm wound of the left atrial appendage. We closed the cardiac wound with 2 separate stitches (3-0 Prolene), then we performed a large pericardotomy, evacuating about 300 ml of blood and clots. Finally we found a small pulmonary injury (about 10 mm wide), for which we performed a pulmonary suture. Postoperative outcome was uneventful, the patient being submitted to multiple echocardiographies during cardiac follow-up without pathologic findings

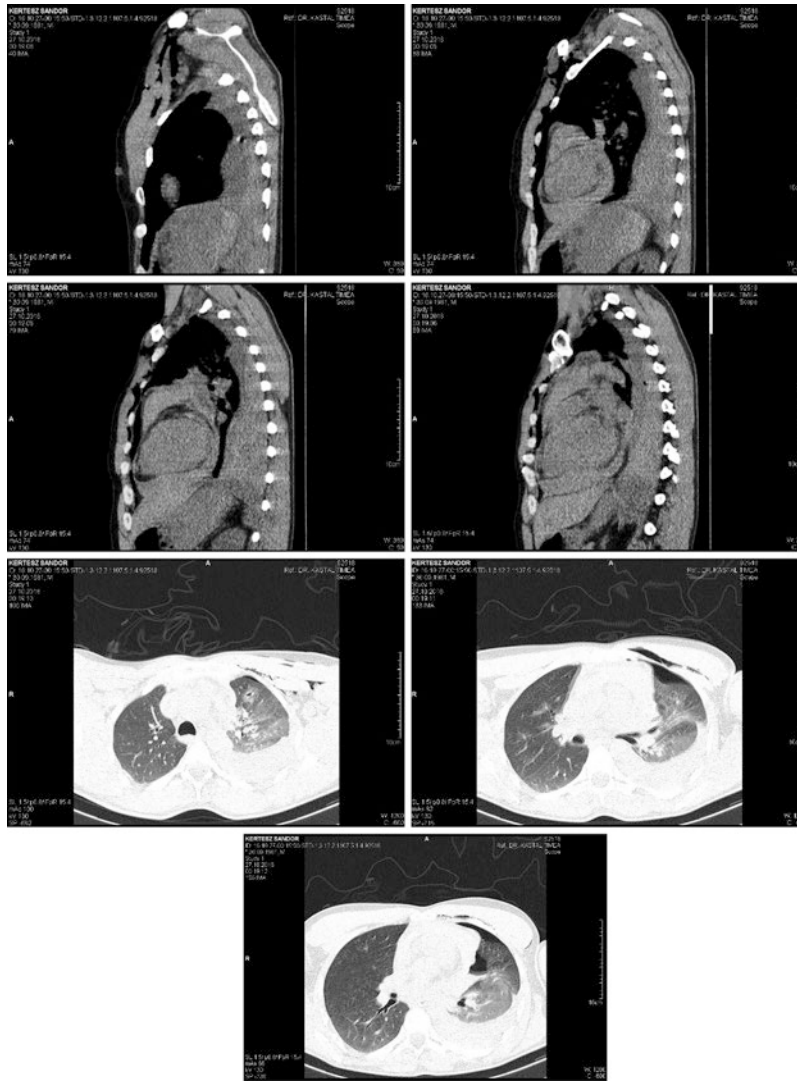
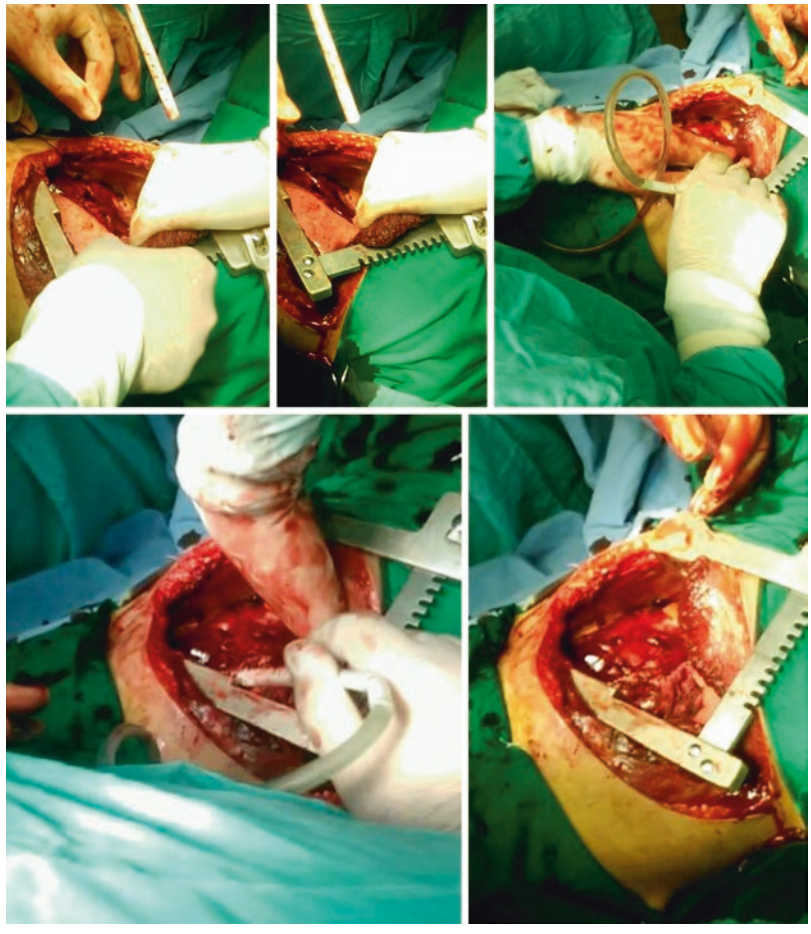


Fig. 14 (continued)



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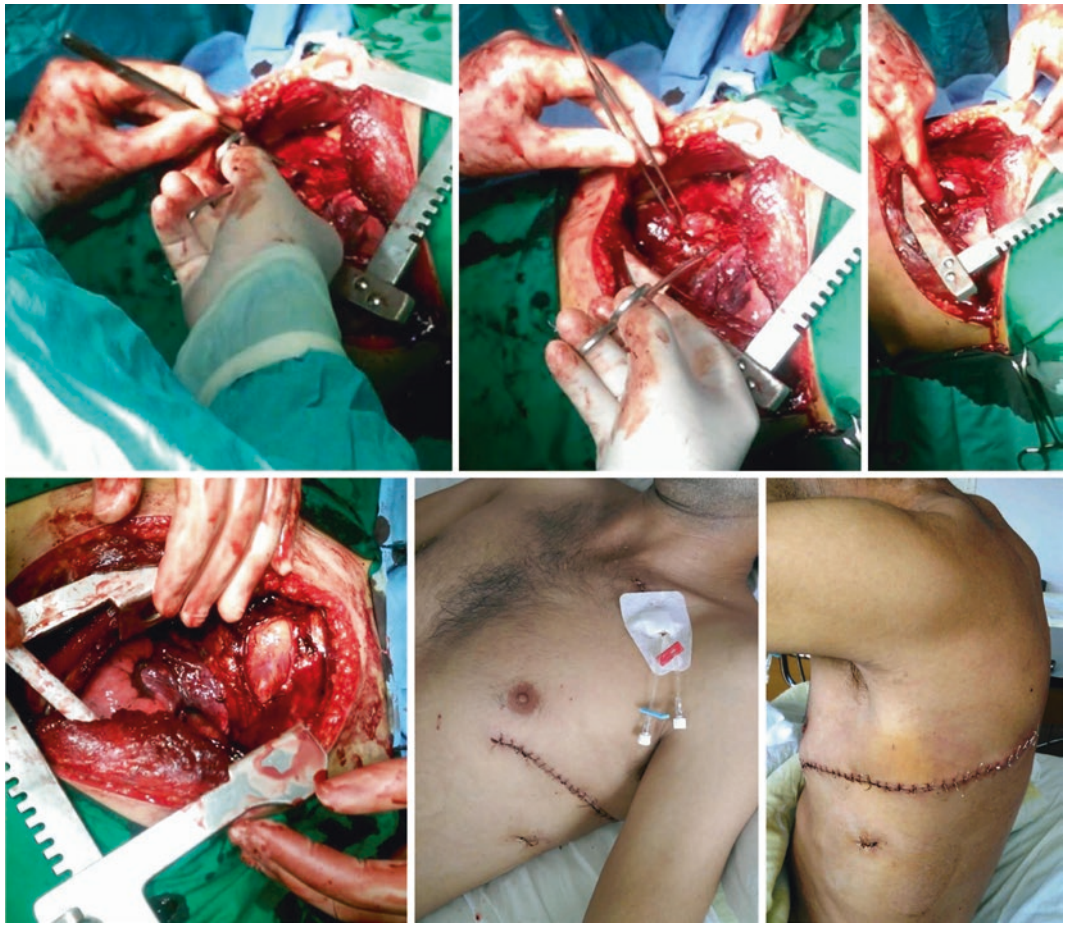

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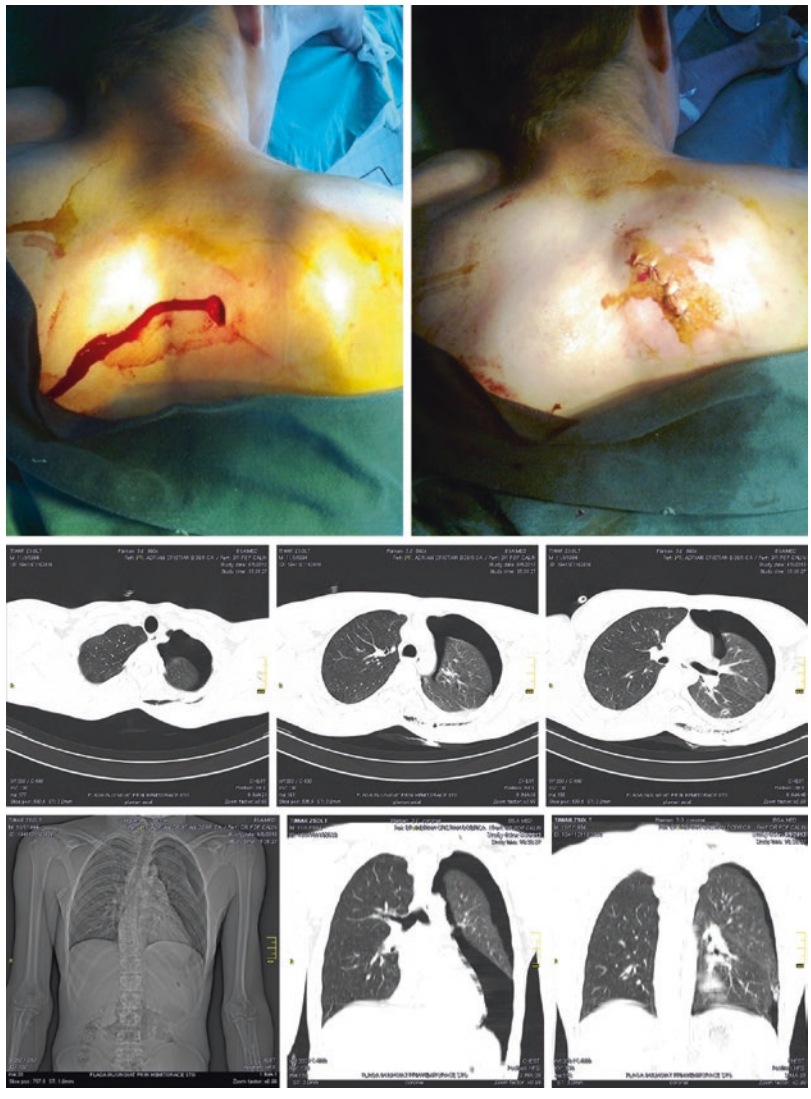

Fig. 15 Right interscapulovertebral penetrating stab wound (knife) in a 17 y.o. male, treated with wound closure (after exploration) and tube thoracostomy

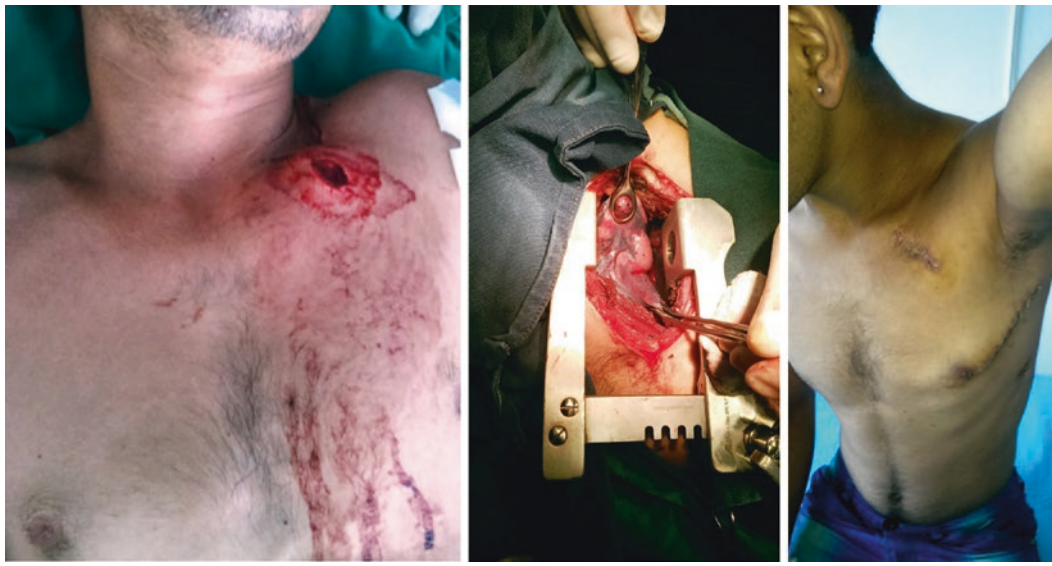

Fig. 16 Left subclavicular penetrating stab wound in a 21 y.o. male, with left upper apical segment injury, treated with pulmonary suture via an anterolateral thoracotomy

with absorbable sutures or with staples (Figs. 16 and 17).

Bleeding tracts should be opened with a GIA stapler, and bleeding points should be ligated one by one. To avoid an air embolism produced by positive pressure ventilation, simple closure of the entrance and exit wounds of the lung parenchyma is contraindicated. The more central the injury, the higher the risk of air embolism.

Resection of bleeding area of the lung may be necessary. We have to avoid anatomical resection in favor of a simple wedge resection, especially in peripherally located injuries (Figs. 18, 19, 20, 21 and 22).

Uncontrolled parenchymal or hilar bleeding, or complex hilar injuries with massive air leaks, should be controlled with hilar clamping or "hilar twist" and attempted repair. Pneumonectomy should be performed only as a last resort because it is associated with a very high mortality rate (up to 90%) [4, 6].

The technique of pulmonotomy (sometimes called "tractotomy") is used when the site of blood loss has been a stab wound deep

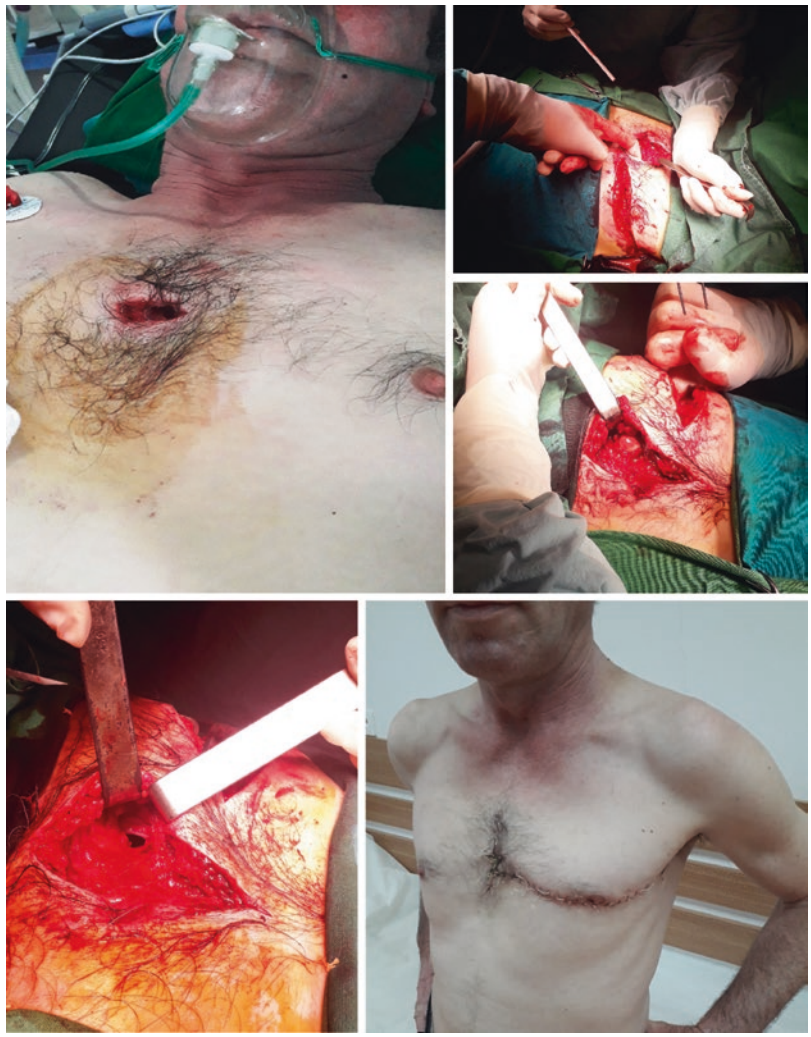

Fig. 17 Precordial wound produced by cow aggression (horn), entering thorax in the 4th intercostal space between sternum an internal mammary vessels with open pneumothorax. An anterolateral thoracotomy was performed finding a laceration of left lower lobe, which was treated with betadine toilet and pulmonary suture

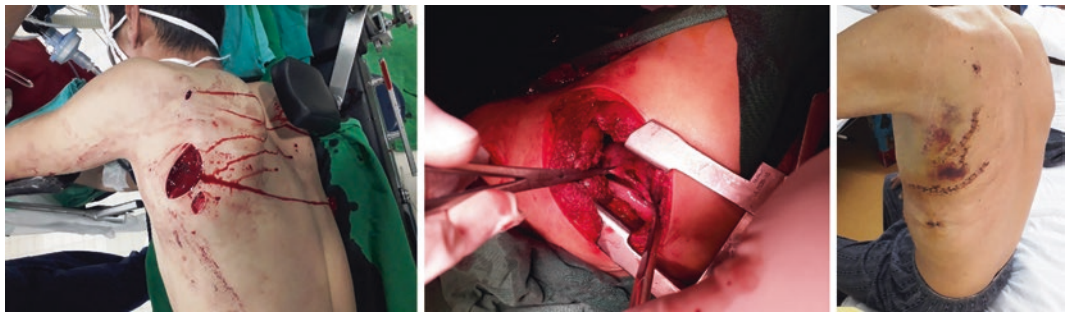

Fig. 18 Left parascapular penetrating stab wound in a 35 y.o. male, associated with multiple non-penetrating chest wounds, with open pneumothorax and a large injury of segment VI, treated with wedge resection

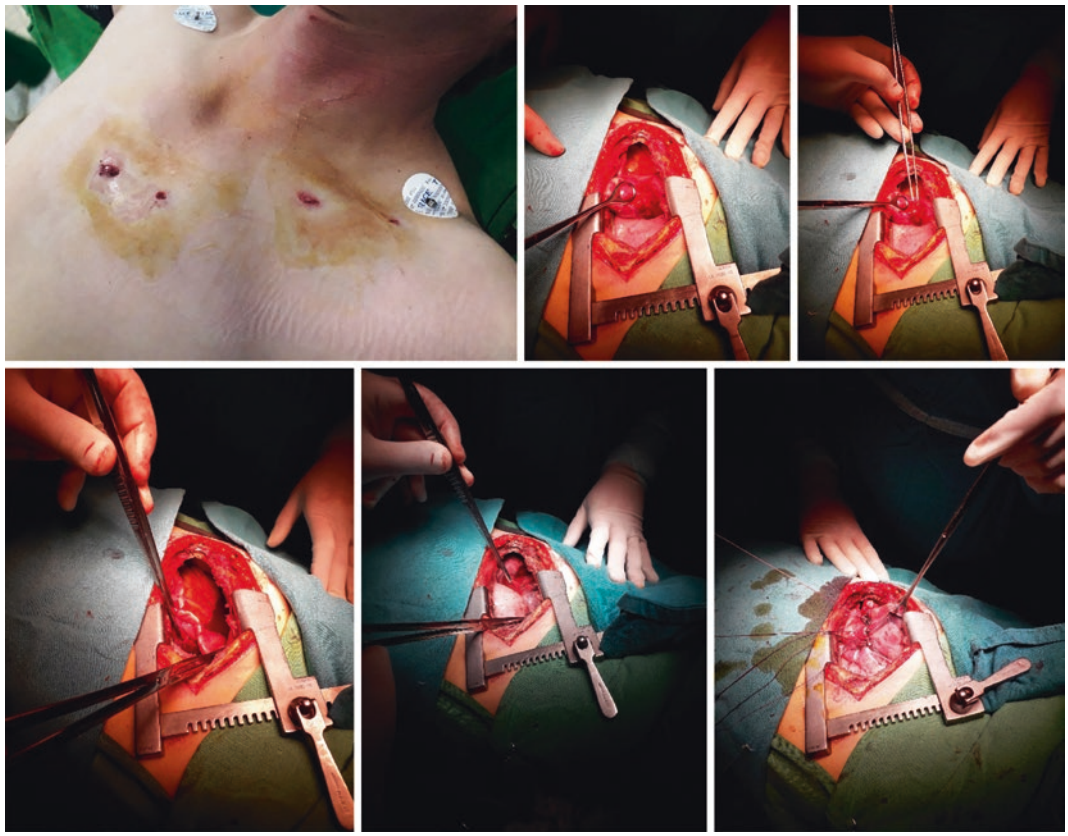

Fig. 19 Multiple stab wounds of the anterior chest wall in a 32 y.o. male, one of them penetrating through the 4th left intercostal space parasternal, with a giant hematoma of the left upper ventral segment associated with multiple lung lacerations, treated with wedge resection associated with pulmonary suture

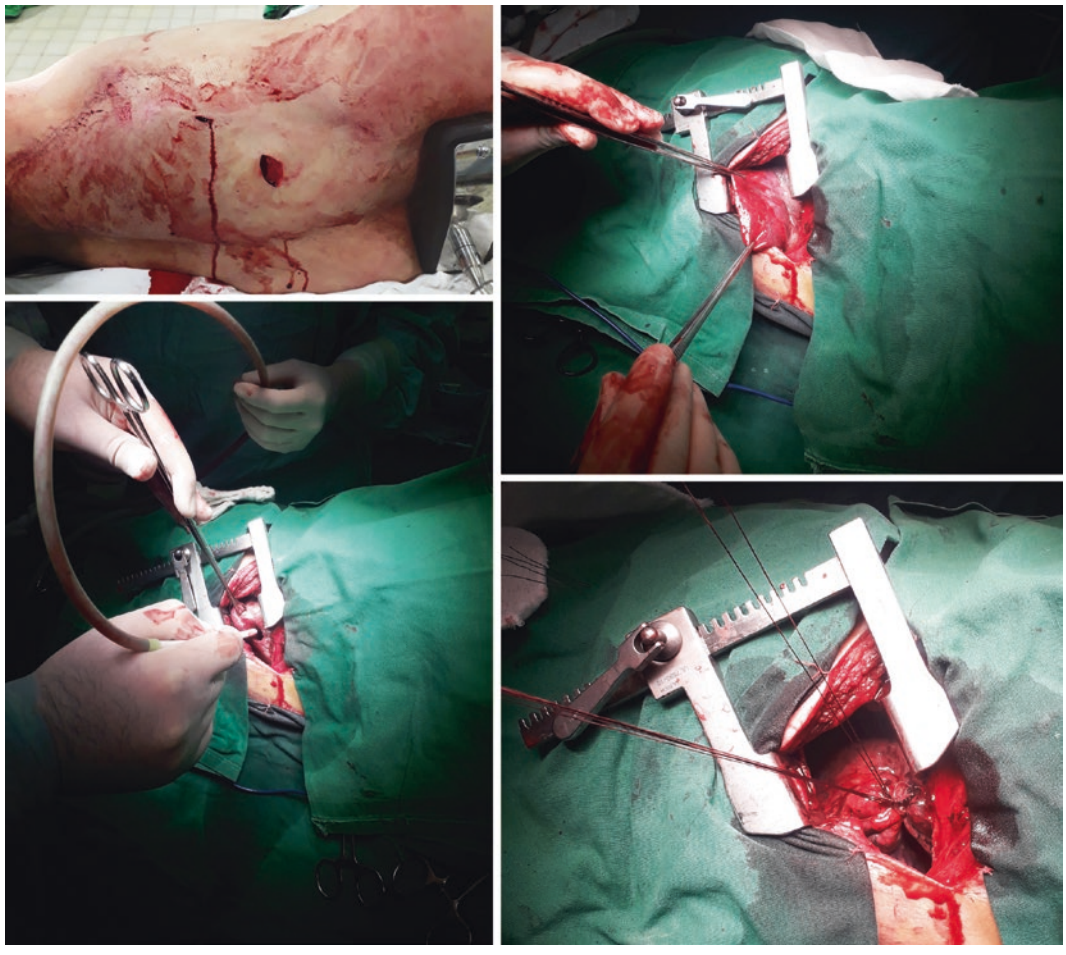

Fig. 20 Penetrating chest stab wound of the left lateral thorax in a 35 y.o. male, associated with a non-penetrating chest wound, with a large injury of segment VI and giant hematoma of the left basal pyramid, solved by wedge resection associated with pulmonary suture

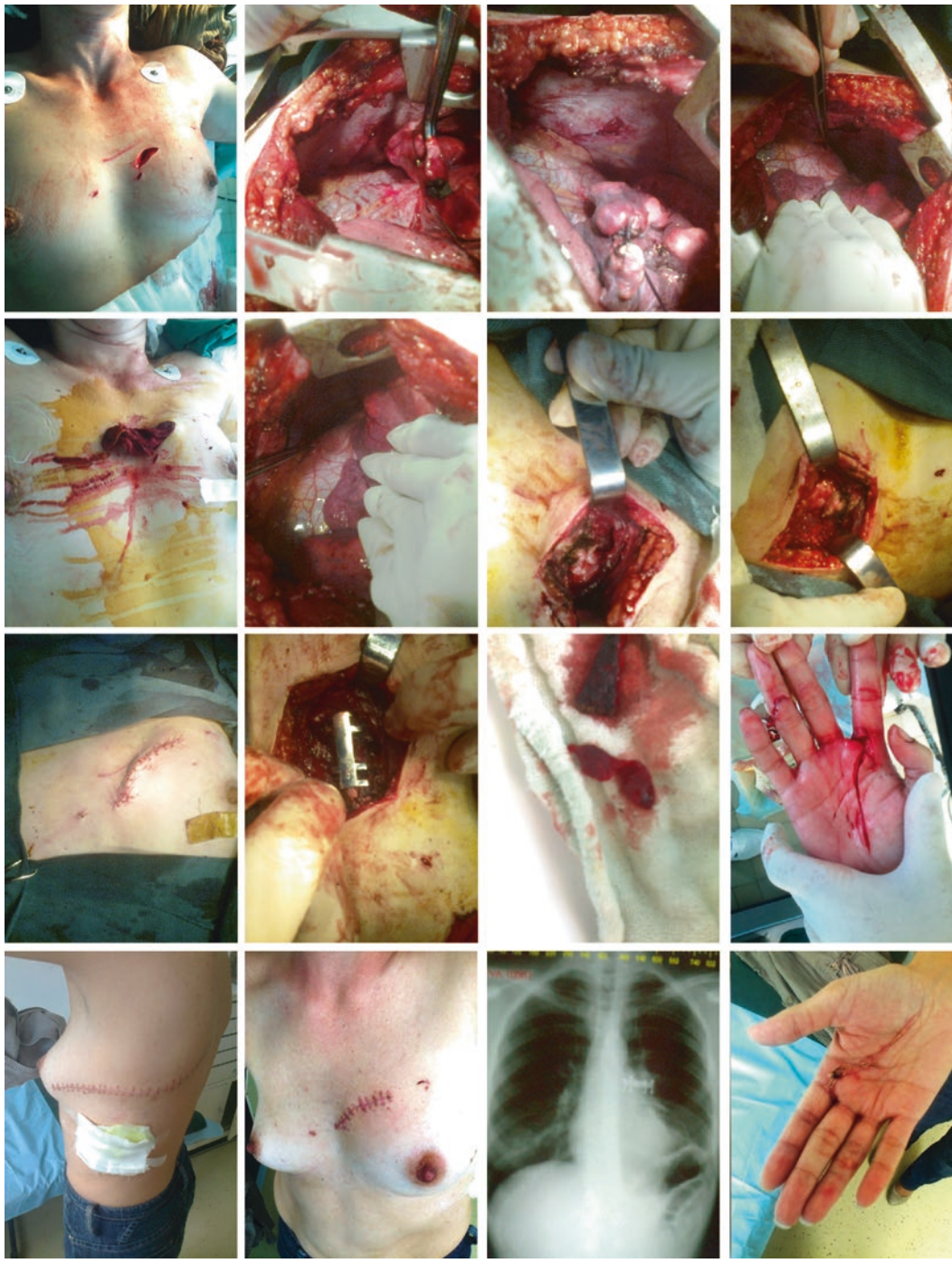

Fig. 21 Multiple chest wall stab wounds after domestic fight in a 35 y.o. school teacher, one of them entering pleura in the 3rd intercostal space parasternal cutting the 3rd rib cartilage, with open pneumothorax, left upper ventral segment injury and pericardial injury. Through a posterolateral thoracotomy we performed wedge resection of the affected segment and exploration of heart (pericardial window starting from the injury) without finding any other injuries. After repositioning the patient we performed reconstruction of the affected rib using a Judet plate and we repaired the wound of the right hand. Postoperative outcome was uneventful with rapid recovery and social reintegration

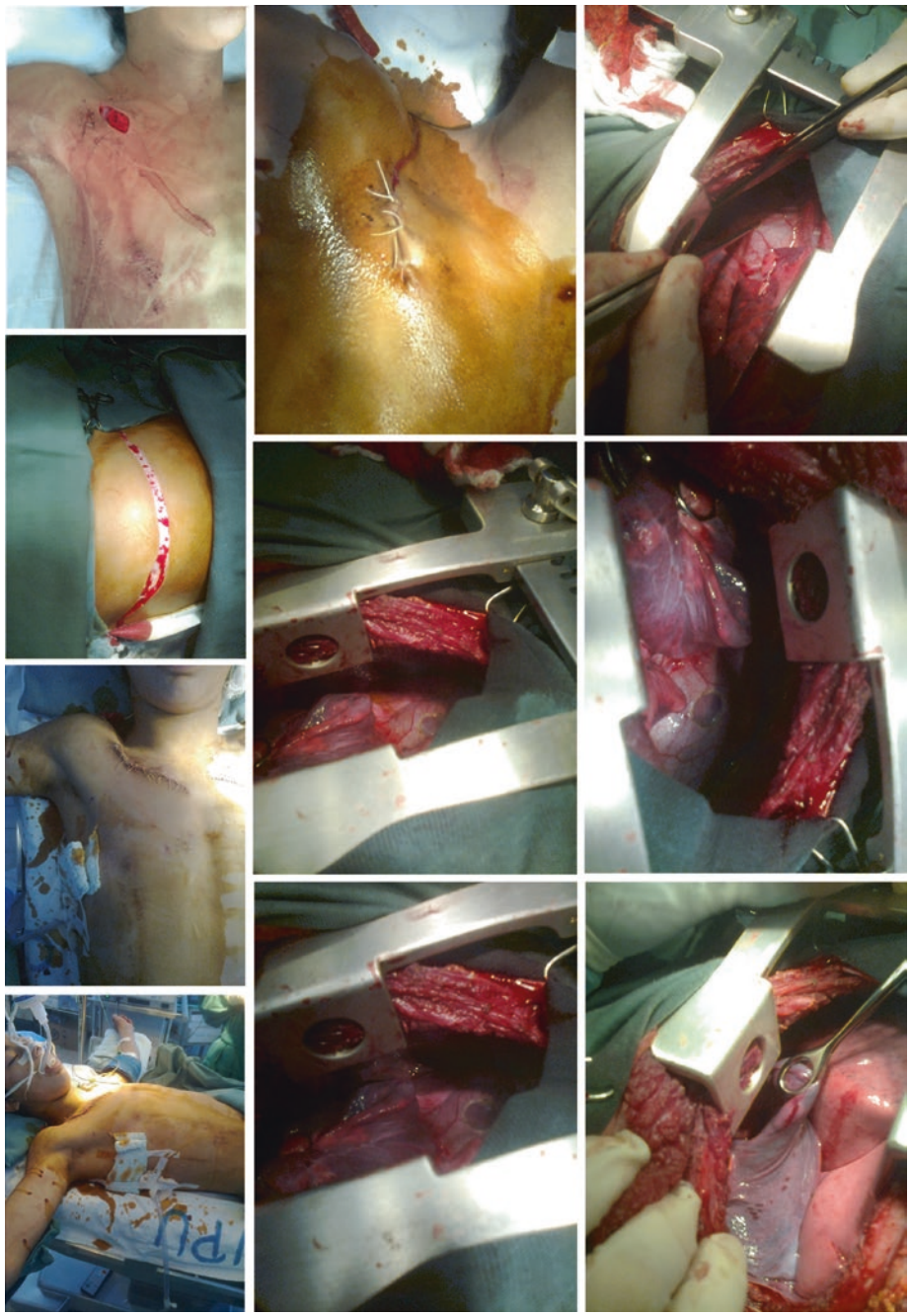

Fig. 22 Right penetrating chest wound with longitudinal cutting of the 2nd rib cartilage, in a 13 y.o. male (who was stabbed by a 12 y.o. boy), with pericardial involvement and right upper lobe injury. After temporary closure of the stab wound, through a posterolateral thoracotomy we found an upper lobe injury associated with a pericardial injury. We performed a pulmonary suture and exploration of the heart (pericardial window starting from the wound) without finding other injuries. After repositioning the patient we performed reconstruction of the affected cartilage with sutures. The postoperative course was uneventful

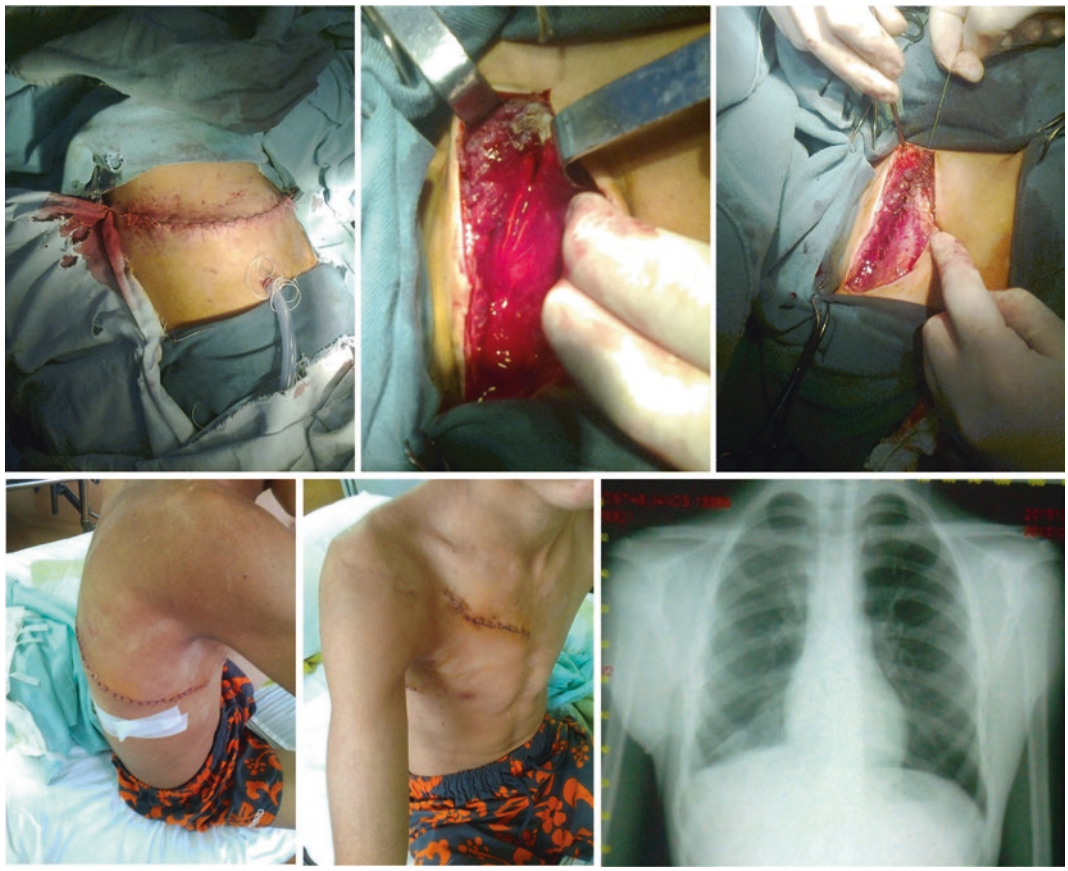

Fig. 22 (continued)

into the pulmonary parenchyma or a gunshot wound completely through a lung lobe [4]. Pulmonotomy is performed to expose and to ligate injured parenchymal vessels through a division of the pulmonary parenchyma between non-crushing clamps or by using a cutting device and a linear stapler. After selective vascular ligation, the pulmonary parenchyma is closed using a continuous 2–0 absorbable suture, with or without reinforcement material added to the staple line, as needed [3].

Management Diaphragmatic Injuries

Penetrating injuries of the chest are very often associated with diaphragmatic injuries, especially on the left side, and small lesions, sometimes missed during initial imagistic exploration, carry the risk of intestinal herniation and incarceration many years after injury.

An injury of the diaphragm may be suspected based on the anatomic location of the wound on the chest wall and predicting the trajectory of the 'weapon' (e.g. knife, projectile). Penetrating wounds of the diaphragm are often associated with injuries of the stomach, spleen, colon, small bowel, liver kidney and retroperitoneal vascular structures [1].

Stab injuries appear twice as often on the left diaphragm compared to the right, most likely because the attacker is usually right-handed and is generally aiming at the left side where the heart is.

Depending of the extent of damage, the repair of the diaphragmatic defect ranges from direct/simple closure to plastic reconstruction (Figs. 23, 24, 25 and 26) [2].

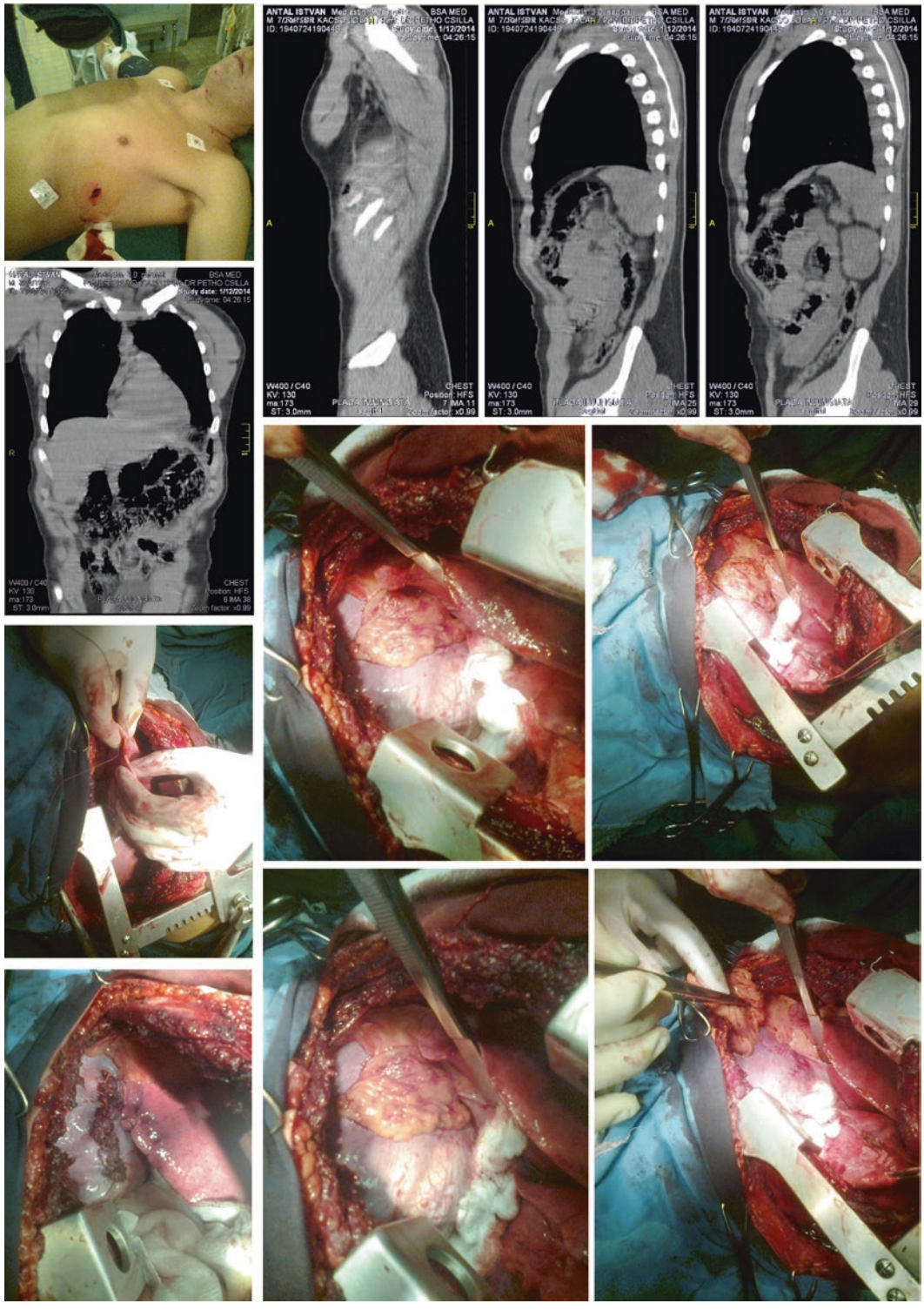

Fig. 23 Left penetrating stab wound entering thorax through the 7th intercostal space in the anterior axillary line, with diaphragmatic injury and left upper lobe injury. Through a posterolateral thoracotomy we performed phrenotomy with exploration of the upper abdomen, *phrenorrhaphy* with separate stitches and pulmonary suture. Postoperative outcome was uneventful

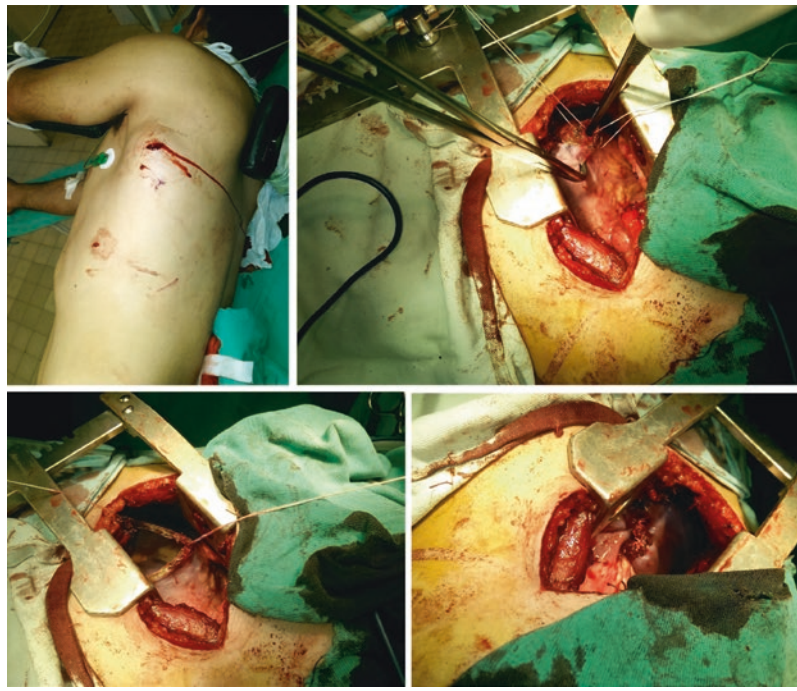

Fig. 24 Left penetrating stab wound entering thorax through the 8th intercostal space in the midaxillary line, with diaphragmatic injury and left lower lobe injury. Through a lower posterolateral thoracotomy we performed phrenotomy with exploration of the upper abdomen, *phrenorrhaphy* with separate stitches and pulmonary suture. Postoperative outcome was uneventful

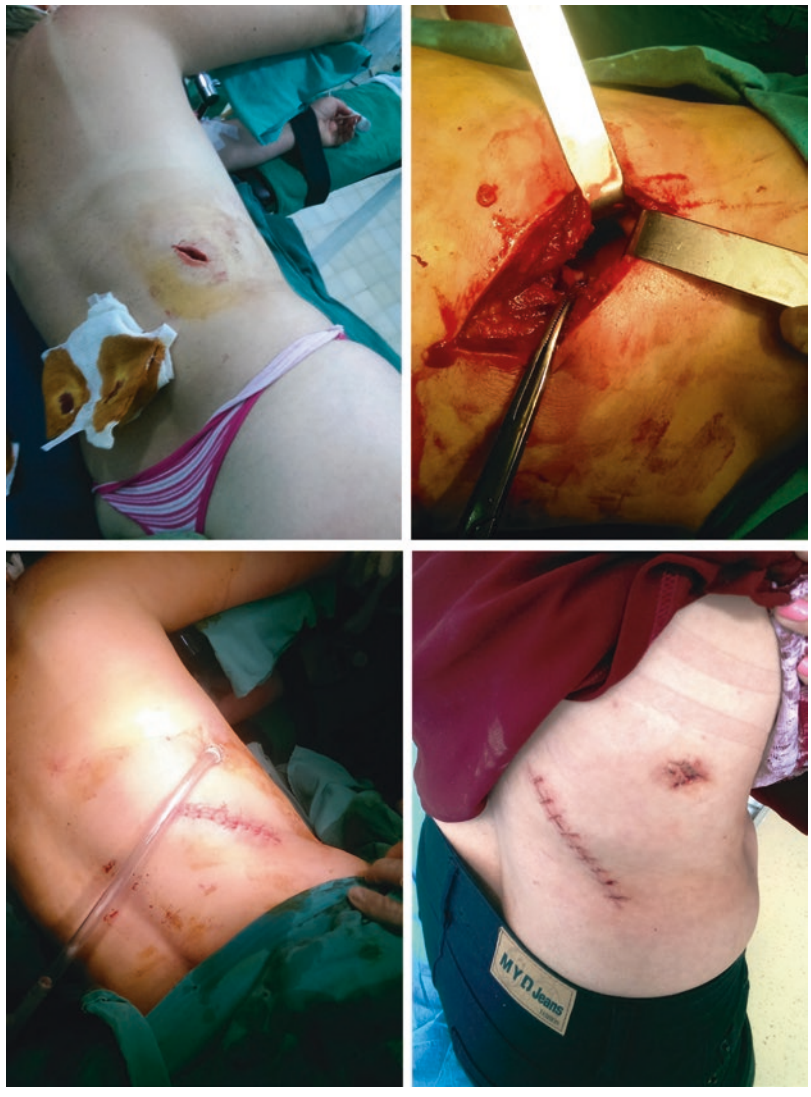

Fig. 25 Right basal stab wound (domestic accident) entering thorax through the 10th intercostal space in the posterior axillary line, with diaphragmatic injury and left lower lobe injury. Through a lower thoracotomy we performed phrenotomy with exploration of the liver followed by *phrenorrhaphy* with separate stitches. Postoperative outcome was uneventful

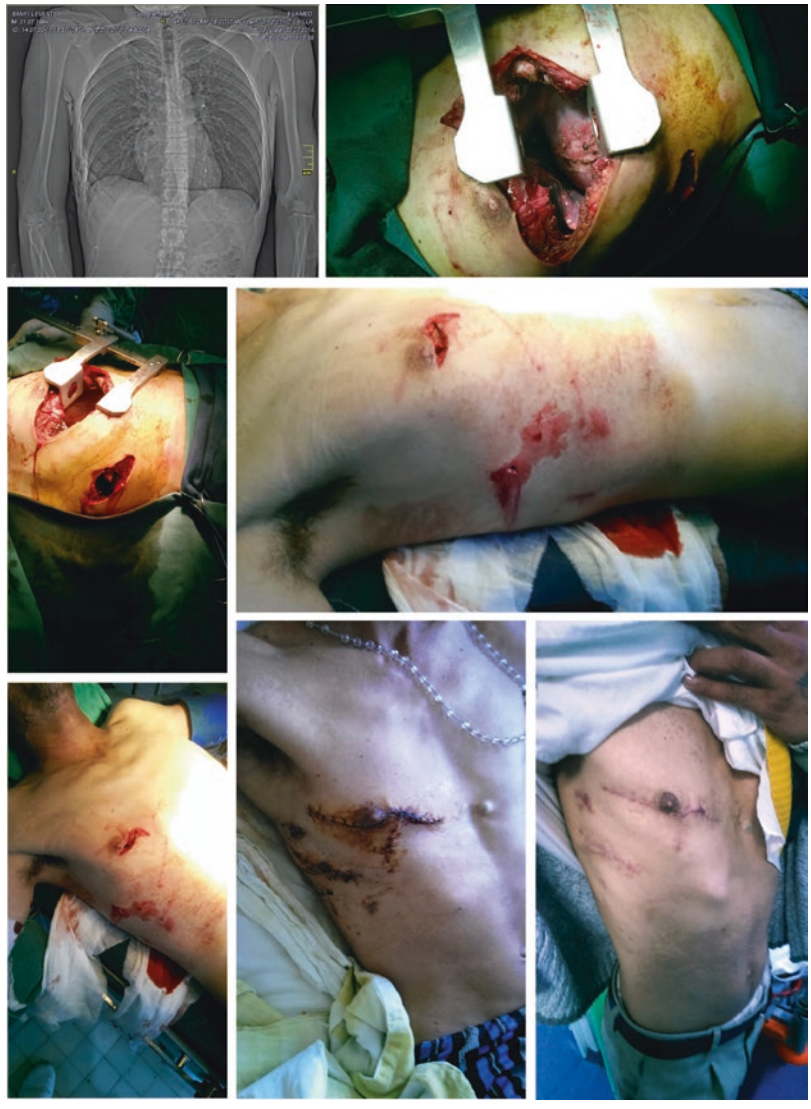

Fig. 26 Multiple bear bites of the left anterior and lateral thorax in a 29 y.o. male, with open pneumothorax, pulmonary and diaphragmatic injuries and multiple rib fractures. First we started with an anterolateral thoracotomy through which we performed cleaning of the pleural cavity and pulmonary suture. The diaphragm presented non-penetrating tears so we didn't performed phrenotomy. After that an extensive excisional debridement of all non-penetrating wounds was performed, followed by repair of the chest wall. Postoperative outcome was uneventful

Thoracic Minimally Invasive Surgery in Open Thoracic Trauma

Penetrating thoracic wounds usually require urgent thoracotomy. Under certain circumstances, thoracotomy may be replaced by a minimally invasive approach, for example when a diaphragmatic wound is suspected.

Self-study

1. Open thoracic trauma includes
   a. Blunt traumas of all type
   b. Penetrating injuries of the chest
   c. 'Piercing through' injuries of the chest
   d. Sternal fractures.
2. Pulmonary injury management includes
   a. tube thoracostomy
   b. tractotomy
   c. lobectomy
   d. wedge resection.

Answers

1. Open thoracic trauma includes:
   a. Blunt traumas of all type
   b. Penetrating injuries of the chest- CORRECT
   c. 'Piercing through' injuries of the chest- CORRECT
   d. Sternal fractures.
2. Pulmonary injury management includes:
   a. tube thoracostomy—CORRECT
   b. tractotomy—CORRECT
   c. lobectomy—CORRECT
   d. wedge resection—CORRECT.

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Damage-Control Thoracic Surgery

Atakan Erkılınç and Mehmet Oğuzhan Özyurtkan

Key Points

To give information about life-saving approaches to blunt thoracic trauma patients; to understand pathophysiology of lung injury.

Introduction

Thoracic trauma is the cause of trauma-related casualties if about one quarter of the civilian trauma deaths. Many of these deaths can be prevented by appropriate diagnosis and adequate management. Although life-saving procedures, including a simple drainage of the pleural space by tube thoracostomy, can decrease the mortality rate of the thoracic trauma, nearly 25% of the patients with penetrating thoracic injury require operative intervention [1].

The initial assessment and treatment of patients with thoracic injury consist of primary survey (airway, breathing, and circulation), resuscitation of vital function, detailed secondary survey and definitive care [2]. "When to intervene" is still a big question for the surgeon, and depends on the patient's physiological status upon arrival. In summary, the main goal of thoracic damage-control is to perform the definitive repair by using fastest and easiest techniques, to overcome the effects of hypothermia, acidosis and coagulopathy [3].

The strategy of damage-control emerged during naval battles in World War II. It was observed that if severely hit ships continued to fight there were major casualties. But when the attention was given to extinguish fires, keep the ship running, and to retreat while covered by other friendly ships, it was reported that there were minor casualties [4]. This strategy has been adopted in trauma surgery, and firstly used in damage-control approach to abdominal trauma, and the use of abbreviated laparotomy is widely accepted. The aim in this situation is to control the bleeding and restore the physiological status of the trauma victim. The centerpieces of the damage control philosophy are the correction of hypothermia, acidosis, and coagulopathy [5]. The adopted strategy in damage-control consists of making minimum necessary interventions (to stop bleeding and to control the contamination) in a very short time, and making the patient to obtain physiologic normality before a definitive re-intervention [4, 5].

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Damage-Control Thoracotomy

Although the principles of abdominal damage-control surgery are well-defined, damage-control for thoracic injuries offers two different approaches for surgeons. The first approach is to provide rapid but definitive repair of heart, lung and esophageal injuries. Thus, this approach has a potential to avoid a second return to the operating room, since the hemostasis is attained during the first operation. The second approach is similar to the abovementioned abdominal damage control, and includes temporary measures that precede a planned operation for a definitive repair [5]. In summary, the primary objectives of damage-control thoracotomy are to release cardiac tamponade, control intrathoracic bleeding, control massive air embolism or bronchopleural fistula, permit open cardiac massage and to allow for cross-clamping of the descending aorta [6].

The standard incision for a damage-control thoracotomy is a left anterolateral thoracotomy. The aim is to gain access to the thoracic cavity in not more than 1–2 minutes. Incision begins from the left side of sternum curving below left nipple and extends to the left midaxillary line at fifth intercostal space. The muscles of the chest wall are quickly divided with a knife down to the level of the intercostal muscles. The intercostal muscles are divided large enough for two fingers to be inserted into the thoracic cavity so as to avoid lung laceration. A Mayo scissors is used to open the entire thoracic cavity. When the visualization is not enough or the wound is transthoracic, the sternum can be divided using a Lebske knife or a pair of trauma shears. But this maneuver will cause the transaction of the internal mammarian arteries, which will start to bleed following restoration of blood pressure, and will need clipping or ligation. A chest wall retractor is placed and opened. Now a very quick assessment is required. The left hand is placed poster lateral to the lung with the palm against the lung parenchyma and compress the lung tissue anteromedially. This maneuver provides the visualization of the descending thoracic aorta. If needed, the aorta can be cross-clamped with a vascular clamp after opening of the mediastinal pleura. The presence of pericardial tamponade is checked at the same time, and should be released by opening the pericardium. The pericardium should be opened longitudinally to preserve the phrenic nerve, which runs along its lateral border. The heart is delivered from the pericardial cavity and any cardiac defect can be temporized with digital control. The defect in the heart can be managed with a polypropylene suture, by inserting and inflating a Foley catheter, or by using even a skin stapler [2, 7].

A vascular clamp placed around the hilum or twisting the lung 180° on its axis may prevent temporarily any exsanguinations from the lung or a massive air leak [8]. In case of a bleeding from the thoracic outlet, placement of a Foley catheter with a 30 cc balloon through the wound tract and traction against the chest wall at the first rib may tamponade the injured vessel [9]. If this bleeding vessel is visible intrathoracically a vascular clamp may also be used, or even digital compression may diminish or stop the bleeding. Once bleeding, pericardial tamponade and massive air leak are temporarily controlled during the damage-control thoracotomy; the patient is taken to the operating room for definitive repair [7].

Operating Room

The patient is placed in supine position with both upper extremities extended laterally and slightly cephalad in the operating room. The patient is prepped and draped with betadine solution from the neck to the knees so that the groin is ready for a vascular conduit. Warming blanket or device may prevent the heat loss. The amount of fluid and blood required for resuscitation is difficult to predict, so blood should be readily available in the operating room. Each 1 ml of blood loss should be replaced with 3 ml of crystalloid fluid in short time management according to the guidelines. An arterial line is placed for invasive hemodynamic monitorisation [2, 7]. Double-lumen endotracheal tube placement is generally not a practical option

in such patients; therefore anesthesiologist can use either a bronchial blocker or perform a mainstem intubation, if unilateral deflation is required for a better visualization [7].

Cardiac Injury

Most patients with cardiac injuries die at the scene. Penetrating trauma is the most common in those who arrive alive at the emergency room. Such a patient is often unstable and necessitates a thoracotomy in the emergency room [4]. Cardiac tamponade is detected based on the presence of Beck's triad (venous pressure elevation, decline in arterial pressure, and muffled heart sounds). Echocardiography or focus assessment sonogram in trauma may help in the diagnosis. When the thorax is opened for emergency purposes, a quick look for tamponade is advised. But it is still proposed to open the pericardium in case of any doubt [2].

Cardiac defects can be temporized with digital compression [2]. Also some maneuvers to stabilize the cardiac movements during repair can be used. These include application of stitches in the heart apex which are then used to traction, or the application of Satinsky vascular clamp [10].

Ventricular wounds can be temporarily controlled by Foley catheter introduced through the wound and inflated [7]. Repair of the ventricles can be done using 4-0 or 5-0 polypropylene suture [4, 5]. Primary control of the ventricular wounds can be managed using even skin staplers [11]. Atrial wounds are more friable. After the initial control they can be repaired with continuous nonabsorbable suture [7]. Intracardiac lesions (sepal defects and valve injuries) necessitate the use of cardiopulmonary bypass. Also coronary artery injury can be repaired with off pump bypass grafting, where the saphenous vein is the conduit of choice [12].

Intrathoracic Vascular Injury

Intrathoracic vascular injuries necessitate a good exposure to gain optimal proximal and distal control. A patient requiring damage-control thoracic surgery has already an anterolateral thoracotomy. This incision may allow for good proximal control, but may be inadequate for distal control or exposure. Thus, a median sternotomy or supraclavicular extension, even a trapdoor incision may be required [7]. When the distal control is difficult to obtain, a Fogarty catheter placed under direct vision or a balloon angioplasty catheter may be used for endoluminal tamponade [13].

After adequate exposure, primary repair of the vessel can be performed, or a graft can be placed. If the vessel is greater than 5 mm, the conduits of choice are polytetrafluoroethylene or knitted Dacron [12]. A temporary shunt can be used if there is no space to suture the graft [14]. Small aortic injuries can be directly sutured using 4-0 nonabsorbable suture. Larger aortic wounds may require digital occlusion or cardiopulmonary bypass [2]. Subclavian arteries can be ligated because they have a rich collateral circulation network in the shoulder girdle [4]. Jugular or innominate vein injury can be repaired with lateral venorraphy or ligating [7].

Lung Injury

Most patients with lung injury do not necessitate thoracotomy, and a simple chest tube placement is mostly enough in the management. Since the pulmonary vasculature houses a low-pressure system and the lung tissue is rich in thromboplastin, massive bleeding in lung after trauma is less common [4]. The abbreviated techniques for the repair of lung injuries depend on the location of the injury, and include pneumonorraphy, wedge resection, tractotomy, lobectomy and pneumonectomy [2, 5, 7]. Lung injuries can be classified as tunneling injuries that do not reach the hilum, hilar injuries, and diffuse parenchymal injuries [4].

Pneumonorraphy (simple closing of entrance and exit wounds) may be used in tunneling injuries. But this may cause ongoing bleeding within the lung parenchymal leading to hematoma

and infection. Ideally when the wound does not proceed to the hilum, the quickest way to gain control of bleeding is to perform a pulmonary tractotomy. The lung bridging to wound is opened with a linear stapler or between two long vascular clamps, and selective ligation of bleeding or air leak points are done [2, 4, 5, 7]. Peripheral bleeding and air leaking lesions may be resected using staplers [5, 15].

When the injury reaches the hilum, the victim is extremely ill upon admission. There may be profuse bleeding and massive air leak. This situation can be temporarily managed by vascular clamp placement around the hilum or by twisting the lung 180° on its axis after dividing the inferior pulmonary ligament [8]. If the surgeon thinks that placing the clamp may take time (due to massive bleeding affecting better visualisation or if the surgeon is not well qualified enough), "hand-over-hand" method is proposed [16]. This technique requires two surgeons, one will quickly clamp the hilum manually while the other evacuates blood from the thoracic cavity, divides the inferior pulmonary ligament, and thereafter prepares for hilar clamping.

An injury extending to the hilum often requires a lobectomy of pneumonectomy. If time and patient's status allow, the surgeon may try to isolate vessels and bronchi to protect as much as lung tissue. But in some cases, the surgeon must consider early "en mass" clamping of the hilum using a large stapler and taking the specimen quickly out en bloc [5, 16, 17]. Therefore, since the survival after trauma pneumonectomy is variable from 0 to 50%, this should be avoided whenever possible [7].

Sometimes the injury may be so severe that the lung is diffusely bruised or lacerated, and the patient has coagulapathy. Such situations may necessitate pneumonectomy which can be devastating for the patient [4]. An alternative in damage control thoracic surgery is to selectively ventilate the non-traumatized lung and packaging the injured one. When the coagulopathy is corrected, packs are to be removed, and definitive surgery may be applied [18].

Tracheobronchial Injury

The principal step in the management of tracheobronchial injury is to secure the airway. This can be achieved by the placement of an endotracheal tube surgically through the wound itself. If there is time, bronchoscopy-guided placement is suggested. Major air leak can be controlled by clamping the hilum (Fig. 1). Tracheal injury can be repaired primarily without tension. A vascular pedicle, including serratus anterior, latissimus dorsi or intercostal muscles can be used for buttressing of the repair to decrease the likelihood of leak or fistula formation. In times of extremis, bronchial injuries can be managed by rapid anatomical resections (lobectomy or pneumonectomy) [2, 7]. But venovenous extracorporeal membrane oxygenation may be used as a non-operative damage control approach. In this situation, this nonoperative strategy is applied as a bridge to definitive repair, and may allow

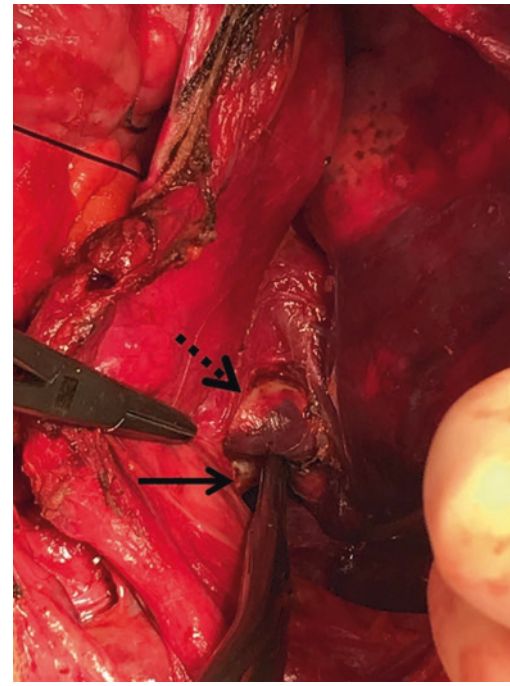

Fig. 1 Clamping of right upper lobe bronchus of a patient with massive hemoptysis. Black thick arrow: right upper lobe bronchi. Dotted arrow: pulmonary artery

to normalise the patient's physiology. Definitive repair then can be done while the patient is supported by venovenous extracorporeal membrane oxygenation [19].

Esophageal Injury

After the diagnosis of esophageal injury, primary repair should be performed if less than 50% of the circumference is injured. The repair needs reinforcement using pleura, intercostal muscle, pericardium or omentum. Larger injuries necessitate exclusion with a cervical esophagostomy and a gastrostomy tube. In patients with exhausted physiologic reserve, alternatively a salem sump can be placed just proximal to the injury along with drainage with a tube thoracostomy tube [2, 7].

Temporary Thoracic Closure

When it is evident that a reoperation will be necessary, a method of temporary thoracic closure by packing can be applied to prevent contamination, achieve hemostasis and not compromise the dynamic balance of the moving structures of the thorax (Fig. 2) [5]. It is also known that once the intrathoracic bleeding has been stopped, major blood loss may later comes from the vascular chest wall. In the early period of the injury, intercostal and internal thoracic vessels' flow may be diminished in a hypovolemic patient. Following the correction of the hemodynamic status of the patient, these vessels start reaching a flow rate of 300 ml per minute, leading to later blood loss [4, 5]. In such cases, towel clips may be placed around the incision to stop bleeding and decrease heat loss, though they are not usually helpful in the former situation. Another option is to en masse closure of chest wall, muscles and skin with a single, running suture line, which provides better hemostasis of the chest wall [5, 7].

Temporary thoracic closure by packing is generally though to impair ventilation, hemodynamics or both [20]. Temporary closure may not be tolerated by an irritable and distended heart, causing hypotension and poor ventilation. To avoid such a situation, the surgeon may prefer using an open urine collection bag or placing packs covered by adhesive drapes in the skin, with application of vacuum technique [21]. The results of some reports also demonstrated that there was no significant difference in the airway pressure before and after the temporary closure [21, 22].

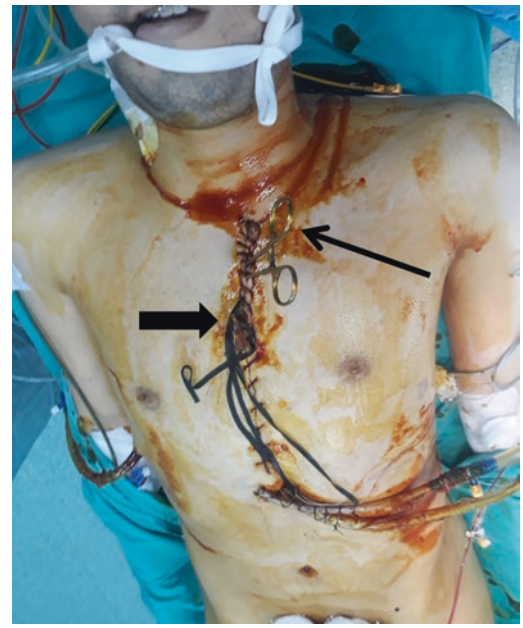

Fig. 2 Patient presented with massive blunt thoracic trauma and right upper lobe laceration. Sternum is left opened but skin incision is closed. Satinsky clamp and vascular snear is observed. Black thin arrow shows Satinsky clamp over right hilum. Black thick arrow shows snear around superior pulmonary artery

Postoperative Care in the Intensive Care Unit

The postoperative care is as challenging as the initial operation. The patient is rapidly transferred to the intensive care unit to further correction of hypothermia, coagulopathy, and acidosis [2, 5]. Infusion fluid warming, increasing the room temperature and warming of irrigation fluids may be helpful [2]. Ongoing bleeding in

such patients is a very challenging problem. It is mostly difficult to determine whether the bleeding is surgical in nature or because the patient is cold and coagulopathic. The decision of returning the patient to the operating room in case of nonsurgical bleeding depends on the surgeon's judgement, since the outcome may be fatal [2, 7].

Patients who underwent temporising approaches including shunting of vasculature, ligation of the vasculature with planned bypass or those requiring more formal esophageal repair should return to the operating room, when their physiologic criteria have been corrected. Hemostasis and definitive closure of the chest wall can be done at this time [2, 7].

Self-study

1. Which statement is false about damage-control thoracotomy:
   (a) The standard incision is a left anterolateral thoracotomy.
   (b) The patient should not always be transferred to the operating room form the second look following damage-control thoracotomy.
   (c) Damage-control thoracotomy is performed to release cardiac tamponade, control intrathoracic bleeding, control massive air embolism or bronchopleural fistula.
   (d) Division of the sternum should be avoided since damage-control thoracotomy aims to perform minimum necessary interventions to control bleeding in a very short-time.
2. Lung injury can be managed by:
   (a) A simple chest tube placement in most of the cases.
   (b) Pneumonorraphy in state of tractotomy, since the former has better outcomes.
   (c) Pneumonectomy if the wound affects the hilum.
   (d) Tractotomy in case of peripheral bleeding or air-leaking lesions.

Answers

1. Which statement is false about damage-control thoracotomy:
   (a) When there is no suspicion of the right lung injury, the standart incision of damage-control thoracotomy is a left anterolateral thoracotomy, which helps the surgeon to gain Access to the left lung and pericardium.
   (b) In some cases, damage-control thoracotomy can be performed to provide rapid but definitive repair of heart, lung and esophageal injuries. Since the hemostasis is attained, there may not be a need for a second look, thus the patient can be transferred to the ICU for follow-up.
   (c) The primary objectives of damage-control thoracotomy are to release cardiac tamponade, control intrathoracic bleeding, control massive air embolism or bronchopleural fistula, permit open cardiac massage and to allow for cross-clamping of the descending aorta.
   (d) Although the aim of damage-control thoracotomy is to perform minimum necessary interventions to control bleeding in a very short-time, the surgeon can divide the sternum to obtain better visualization or the injury is transmediastinal. CORRECT.
2. Lung injury can be managed by:
   (a) It is very known that mostly lung injury do not necessitate major surgical interventions, and can be managed by a simple chest tube placement. CORRECT.
   (b) When the wound is not reaching the hilum, pneumonorraphy can be applied, but there is a risk for ongoing bleeding within the lung parenchymal leading to hematoma and infection. Thus the ideal approach is to perform tractotomy.
   (c) Pneumonectomy can be performed if the injury extends to the hilum. But the

survival after trauma pneumonectomy is very low (between 0 and 50%). Thus if the patient's status allow, it is advised to perform lesser resection such as lobectomy.

(d) Peripheral bleeding orair-leaking lesions are not required tractotomy, and can be managed quickly by stapler resection.

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Approaches and Surgical Techniques for Chest Wall Trauma

Alessio Campisi, Luca Bertolaccini, and Franco Stella

Key Points

- Chest wall injuries are common after traumas but rarely need surgery
- Pain control and adequate pulmonary hygiene are essential for patients
- There are no absolute indications for operative management of chest wall injury
- Benefits of surgical therapy are still under examination
- Different approaches and multiple methods of fixation can be used.

Introduction

Chest trauma is a collective term and represents a prominent part of injuries, being a significant source of morbidity and mortality [1]. The ribs are the most commonly injured component of the thoracic cage, occurring in about 10% of chest traumas and 20% of severe injuries; flail chest is anatomically defined as a fracture of at least three or more adjacent ribs in at least two places, creating a part of the chest wall that moves independently with respiration. Sternal fractures are common after high forces being applied directly to the sternum, and they are often associated with cardiac and great vessel injury.

Nevertheless, most patients with chest wall traumas can successfully be treated with a conservative approach or with chest tube insertion for the associated injuries. Different operative techniques, lack of consensus on a classification system and indications for surgery and deficiency of randomised trial studies render surgical rib fracture stabilisation a controversially discussed topic [2]. Anyhow, recently, surgical chest wall repair is taking interest thanks to different case series showing faster recovery and decreased morbidity in patients who had undergone surgical restoration of the chest wall [3].

Historical Perspective

Description of diagnoses and management of chest wall injuries date back to Ancient Egypt [4]. In the modern era, a surgical approach to chest wall injuries started to be considered at the beginning of the 1900s; in 1926, Jones and Richardson described a percutaneous technique for traction of fractured ribs [5]. Since then,

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different techniques of external fixation have been described, all of which showed significant complications. Thus, during the 1960s and 1970s, patients with severe chest wall trauma started to be managed with "internal pneumatic stabilisation" or long-term positive pressure mechanical ventilation. Initially, mortality lowered with this approach; anyhow, complications related to mechanical ventilation such as barotrauma, ventilator-associated pneumonia, and tracheal injury were often encountered. Therefore, in 1975, Trinkel and Colleagues, and then Shackford and Colleagues in 1976, disproved this approach [6, 7], and since then it has been used to compensate concomitant respiratory failure mainly due to pulmonary contusion, but not as a "stabilising" agent per se.

In the last years, multiple surgical methods for repairing rib fractures have been described thanks to much more available rib-specific fixation products and, despite nonsurgical management being still the most common approach, numerous studies show improved outcomes after surgical stabilisation of rib fractures compared with conventional management in the most severely injured patients.

Modern Treatment Strategies

The current modern treatment of chest wall injuries includes non-operative, and surgical treatment strategies, with the latter being indicated in selected cases.

Non-operative Management

Mechanical Ventilation

It has been shown that internal pneumatic stabilisation, using mechanical ventilation, cannot reduce significant deformations and dislocations; thus, according to current recommendations [8], mechanical ventilation should be avoided in the absence of respiratory failure and, when necessary, the patients should be weaned from the ventilator as soon as possible. No single mode of ventilation is best for patients with flail chest or pulmonary contusion. On the other hand it is evident that positive end-expiratory pressure should be used to recruit alveoli. Moreover, some patients may be managed with non-invasive ventilation (NIV); patients should be monitored in the intensive care unit, to be intubated immediately if it is necessary.

Pain Control

Optimal pain control is the key to the treatment of patients with chest wall injuries. It is based on non-regional analgesia, regional anaesthesia, and rib fixation.

Non-regional analgesia is often the first line of therapy for the pain of mild to moderate intensity; this initial approach follows the principles of postoperative pain control recommending multimodal analgesia. It is defined as a combination of analgesics, all of which have different mechanisms of action. This multimodal approach should involve nonsteroidal anti-inflammatory drugs, acetaminophen, and opioids (oral intake preferred over intravenous, patient-controlled analgesia preferred over continuous intravenous analgesia) [9].

Regional anaesthesia consists of intercostal nerve blocks, intrapleural analgesia, paravertebral blocks and epidural catheters. This should be considered for pain control in patients with a high risk of respiratory complications. Risk factors are severe chest wall injury (>4 fractured ribs), >45 years of age, low pulmonary function tests, and/or ineffective multimodal analgesia.

Intercostal nerve blocks with or without a continuous infusion catheter involve the injection of local anaesthetics at the level of the rib fracture plus one rib above and one rib below. Local anaesthetic toxicity, pneumothorax and puncture of intercostal vessels make this modality less favourable.

Intrapleural analgesia consists of the injection of the anaesthetic agent into the pleural cavity through a pleural catheter or an existing thoracostomy tube. It is not a popular modality of pain control because of the necessity of tube

insertion or drainage clamping with the risk of pneumothorax.

The paravertebral block consists of blocking the nerve root in the paravertebral space; it guarantees a reasonable pain control and some advantages compared with epidural blocks, such as no urinary retention and no systemic vasodilation, but it lacks evidence of better outcomes.

Epidural anaesthesia is the most well-studied model of locoregional pain control, showing optimal results in terms of pain control, pulmonary function, complications and mortality [10]. Anyhow, it is technically more challenging than the other regional approaches and carries certain risks (dural puncture and spinal cord injury, hypotension, urinary retention, motor block etc.) and contraindications for placement and removal (coagulopathy, anticoagulation or antiplatelet therapy, thrombocytopenia). Therefore, the use of epidural catheters is still debated.

Respiratory Therapy

Significant pulmonary dysfunction may develop after severe chest wall injury due to pulmonary contusion or loss of respiratory mechanical function from the flail chest. Once more, optimal pain control is mandatory to permit deep breathing and coughing/secretion clearance. Another fundamental component of the management of chest wall injury is the respiratory therapy associated with early mobilisation of the patients. Physiotherapists and bedside nurses play a crucial role. Incentive spirometry, positive expiratory pressure therapy devices and secretion clearance may prevent critical complications, such as atelectasis and pneumonia, which may require mechanical ventilation, creating a vicious circle.

Indications for Surgical Management

In the last years, surgical management of chest wall injuries has become more popular, although it is performed in less than 1% of patients, thanks to multiple studies showing improved outcomes after early surgical fixation [11]. The majority of those papers are not randomised and involve ventilated patients. These studies show advantages in terms of decreased time on mechanical ventilation, fewer days of stay in the intensive care unit, decreased chest infections, decreased chronic pain, better respiratory function tests etc. Therefore, none of the published randomised studies compares operative fixation with a current non-operative multimodal approach.

There are no absolute indications for operative management of chest wall injury. It is generally accepted that a flail chest is an indication for surgery, but not every flail chest necessitates surgical repair. The most common indication for surgical fixation is a respiratory failure in the absence of severe pulmonary contusion in a patient with an anterolateral flail segment; in fact, in the presence of significant pulmonary impairment, the benefits of chest wall stabilisation decay.

Another indication for surgery is a respiratory compromise in non-intubated patients, despite maximal non-operative management. In these cases, chest wall stabilisation improves pain control, respiratory dynamics and secretion clearance.

Other relative indications are pain refractory to medical management, complex rib fractures with the risk of damage of vital structures, symptomatic rib fracture, non-union or malunion, impaired pulmonary function tests owing to chest wall deformity and severe deformity unlikely to heal spontaneously.

Traditionally accepted indications with limited supporting evidence are thoracotomy for other indications and failure to wean from mechanical ventilation [2].

Surgical Approaches

Surgical approaches in patients with chest wall injuries are determined by multiple factors, such as which ribs and how many of them are injured, sternal involvement, presence of flail chest and/or associated injuries etc. It is important to remember that the primary goal of surgery is to stabilise the chest wall to restore the mechanics of breathing, reduce deformity and pain. Patients with severe traumas and flail chest often have

multiple fractured ribs, multifocal ribs fractures and bilateral fractures with sternal damage.

It is usually not necessary to fix all the fractures and all the ribs, but the most displaced and unstable ones, preferentially using just one surgical incision.

Several effective approaches are available to access presumed sites of injury. Axial and three-dimensional reconstructions of computed tomography scans of the thorax are extremely helpful (Figs. 1 and 2) and should be obtained.

The choice of intubation, with a single or a double-lumen endotracheal tube, is based on the presence of associated intrapleural or pulmonary lesions. The position of the patient depends on the chest wall injury: a supine position is preferred for bilateral injuries and anterior flail chest with or without sternal involvement. The lateral decubitus position needed for lateral thoracotomies is contraindicated in hemodynamically unstable patients, in case of severe neurologic traumas or spinal fractures, but it is the preferred position for unilateral chest traumas with associated intrathoracic lesions.

The incision should be selected according to the area to be approached and with the surgeon's experience with that approach, should be large enough to expose all the fractured ribs that will be fixed and should avoid significant muscular division.

The most commonly used approaches are lateral thoracotomy (either anterior or posterior), posterior paramedian incision or inframammary approach.

Fracture of the upper ribs (1–3) are difficult to reach surgically; muscles compensate for any dysfunction, so they are rarely treated in the operating room. Fractures of the lower rib cage (11–12) are rare because of their flexibility and rarely require surgical fixation.

An anterolateral thoracotomy is a preferred approach for anterolateral fractures. The latissimus dorsi should be identified and spared, the fascia of the serratus anterior should be exposed, and the fibres of the muscle dissected along their orientation to expose the periosteum of the ribs. Care must be taken to protect the long thoracic nerve and artery on the lateral border of the serratus anterior muscle.

A posterolateral thoracotomy is a preferred approach for posterior fractures. If possible,

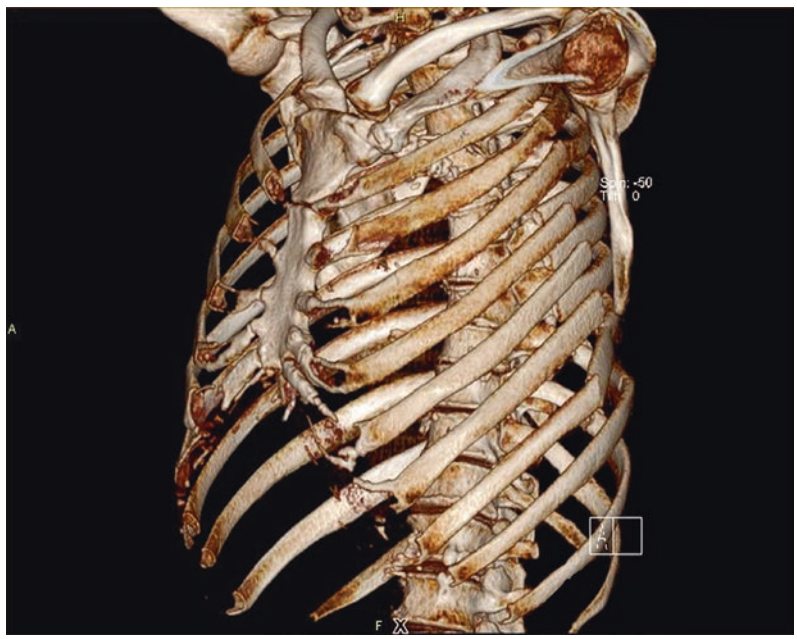

Fig. 1 Three-dimensional reconstructions of computed tomography scans showing multiple left-side rib fractures. [https://commons.wikimedia.org/w/index.php?curid=6511887]

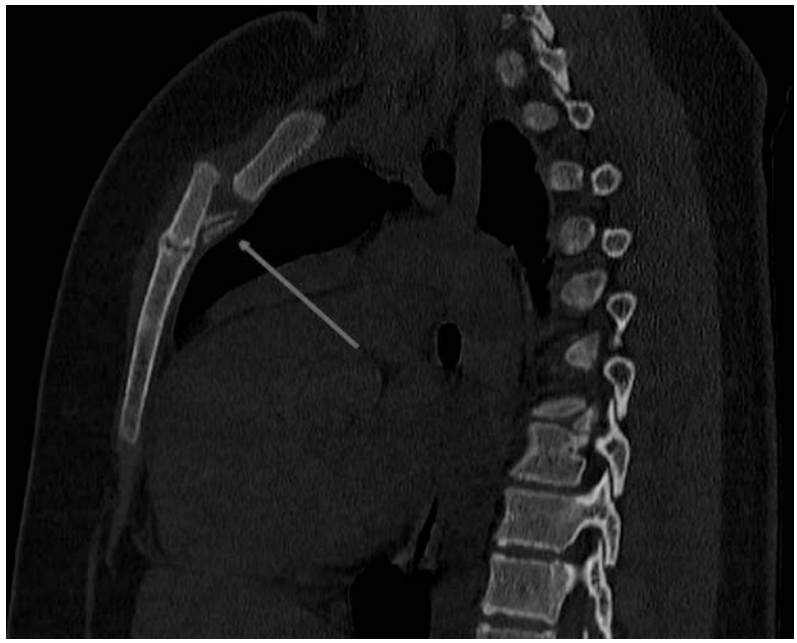

Fig. 2 CT scan. Sagittal plane demonstrating transverse sternal fracture between the manubrium and the sternal body. The green arrow points at a bone fragment located behind the body of the sternum

again the latissimus dorsi muscle should be split parallel with its fibres; the serratus anterior muscle should be preserved. Care must be taken to protect the thoracodorsal nerve and artery.

The posterior paramedian approach is the preferred approach for posterior fractures adjacent to the spine. Deep dissection is carried out to reach the auscultatory triangle with no incision of any muscular fibres.

The inframammary approach is the preferred approach for anterior fractures, eventually involving the costochondral junction or the sternum. The patient is supine, and a submammary skin incision is performed. The breast must be dissected of the pectoralis major fascia and elevated to gain the chest wall. Once again, serratus anterior fibres should be split parallel to reach fractures beyond the anterior axillary line.

Chest Wall Stabilization

Basic principles of treatment for fractured bones consist of first aligning them, which is called reduction, in an anatomic position and then maintaining them in the reduced position until the healing process has created a callus. Surgical stabilisation options include external or internal fixation. External fixation is rarely used in chest wall diseases. Internal fixation requires a device placed directly through an open surgical exposure to stabilise the fracture. There are multiple different types of fixation systems, the majority of them adapted from orthopaedic surgery, such as Kirschner wires, Rehbein plates, Adkins struts etc. A milestone in rib osteosynthesis was the creation of a specific device for thoracic surgery: the Judet staple. Nowadays, materials derived from the manipulation of the Judet staples are the mainstay systems for rib fixation. Generally, it is performed through a single incision, most often a thoracotomy. Moreover, recently, minimally invasive techniques have been reported, but they still lack consensus.

Whatever the skin incision, muscle-sparing approaches are suggested; once the chest wall is reached, the fractures are easily detectable and exposed. The reduction is usually accomplished quite efficiently without damaging

the periosteum and leaving it intact. Aggressive over-exposure of the fractured rib is not necessary.

Despite the multiple systems currently available, the most common fixation method used is titanium plates and screws [12]. Although every material has disadvantages, synthetic materials are readily available, simple to implant and to manipulate; in particular, titanium is extremely biocompatible, malleable, has a high-thermal and mechanical resistance and is magnetic-resonance compatible. Another important innovation derived from orthopaedic surgery is the introduction of locking screws for rib fixation, which allow a stable fixation even in osteoporotic bone. Once the thickness of the ribs is measured, the screws of the right size are chosen to create enough friction between the plate and the bone. The titanium bars are then fixed to the patient's ribs bilaterally using at least three screws to both ends of each plate, taking care to avoid the cartilaginous part of the ribs (Fig. 3). When the chest wall is finally stabilised, a drainage tube is placed in the chest cavity, and the incision closed following the anatomical planes.

Conclusions

Severe chest wall injuries are both, life-changing and life-threatening injuries. Their surgical management is becoming a popular procedure as the limitations and complications of non-operative treatment become apparent. New techniques and products have been developed and will probably continue to evolve rapidly. Anyhow, the exact indications for rib fracture stabilization are still unclear and the benefit of surgical fixation is still under debate, although different studies reported a reduction in duration of mechanical ventilation, length of intensive care unit stays, length of stay in hospital, pneumonia, pain, need for tracheostomy, and overall cost of patient treatment. Despite its potential benefits, at present, only a small part of patients with severe chest injuries receive operative fixation, and non-operative management remains the most common treatment method.

Thus, more clinical studies are needed to determine the timing, the optimal stabilisation techniques and the best devices of surgical management of chest wall traumas.

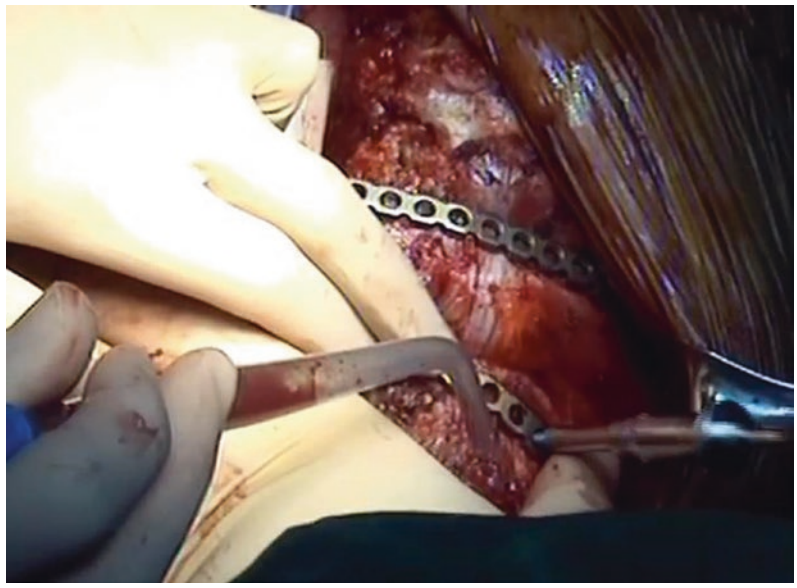

Fig. 3 Anterior flail chest with the involvement of the sternum stabilised using titanium plates

Self-study

1. The best regional analgesia in a patient with a severe chest wall injury is:
   a. Epidural catheter
   b. Intercostal nerve blocks
   c. Intrapleural catheters
   d. Paravertebral blocks
2. Which of the following is NOT an indication for surgery in chest wall injuries:
   a. Respiratory compromise in non-intubated patients
   b. Posterior flail chest
   c. Anterior flail chest with respiratory failure
   d. Severe deformity with uncontrolled pain
3. Which of the following is true about stabilisation of the chest wall:
   a. It restores the mechanics of breathing
   b. It reduces deformity
   c. It reduces pain
   d. All of them
4. Basic principles of surgery for chest wall stabilisation is/are:
   a. To fix the most displaced and unstable rib fractures
   b. An incision centred above the fractured ribs should be made
   c. Avoidance of significant muscular division by the surgeon
   d. All of them
5. Which of the following is NOT true about surgery of chest wall injuries:
   a. Muscle-sparing approaches are suggested
   b. Synthetic materials are commonly used to stabilise the chest
   c. The periosteum of every damaged rib should be removed
   d. Drainage should be left in place in the pleural cavity

Answers

1. The best regional analgesia in a patient with a severe chest wall injury is:
   a. Epidural catheter
   b. Intercostal nerve blocks
   c. Intrapleural catheters
   d. Paravertebral blocks

   CORRECT: A. Epidural is the most well-studied model of locoregional pain control, showing optimal results in terms of pain control, pulmonary function, complications and mortality
2. Which of the following is NOT an indication for surgery in chest wall injuries:
   a. Respiratory compromise in non-intubated patients
   b. Posterior flail chest
   c. Anterior flail chest with respiratory failure
   d. Severe deformity with uncontrolled pain

   CORRECT: B. All of them are indications for surgery except uncomplicated posterior flail chest. Posterior muscular wall and decubitus help with healing and respiratory function.
3. Which of the following is true about stabilisation of the chest wall:
   a. It restores the mechanics of breathing
   b. It reduces deformity
   c. It reduces pain
   d. All of them

   CORRECT: D. The primary goal of surgery is to stabilise the chest wall to restore the mechanics of breathing, reduce deformity and pain.
4. Basic principles of surgery for chest wall stabilisation is/are:
   a. To fix the most displaced and unstable rib fractures
   b. An incision centred above the fractured ribs should be made
   c. Avoidance of significant muscular division by the surgeon
   d. All of them

   CORRECT: D. All of them are basic principles to follow during surgery for chest wall stabilisation.
5. Which of the following is NOT true about surgery of chest wall injuries:
   a. Muscle-sparing approaches are suggested
   b. Synthetic materials are commonly used to stabilise the chest
   c. The periosteum of every damaged rib should be removed
   d. Drainage should be left in place in the pleural cavity

CORRECT: C. All of them are fundamental principles of surgery for chest wall stabilisation expect for the C. The periosteum of any rib should be left intact without any damage if it is surgically possible.

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Correction to: Thoracotomy as the Surgical Route for Synchronous Thoracic and Non-thoracic Procedures

Achilleas G. Lioulias, Michail D. Tsimpinos and Meletios A. Kanakis

Correction to:
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In the original version of the book, the spelling of the author name Meletios A. Kanakis and his affiliation was incorrect.

The corrected name and affiliation is given below:

Meletios A. Kanakis, Department of Paediatric and Congenital Heart Surgery, Onassis Cardiac Surgery Center, Athens, Greece

The correction chapter and the book have been updated.

The updated version of this chapter can be found at https://doi.org/10.1007/978-3-030-40679-0_73

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