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Esophageal Abnormalities

Edited by Jianyuan Chai

ESOPHAGEAL ABNORMALITIES

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http://dx.doi.org/10.5772/65143
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First published in Croatia, 2017 by INTECH d.o.o.
eBook (PDF) Published by IN TECH d.o.o.
Place and year of publication of eBook (PDF): Rijeka, 2019.
IntechOpen is the global imprint of IN TECH d.o.o.
Printed in Croatia

Legal deposit, Croatia: National and University Library in Zagreb

Additional hard and PDF copies can be obtained from orders@intechopen.com

Esophageal Abnormalities
Edited by Jianyuan Chai
p. cm.
Print ISBN 978-953-51-3631-6
Online ISBN 978-953-51-3632-3
eBook (PDF) ISBN 978-953-51-4578-3

Meet the editor

Dr. Chai received his PhD degree from the City University of New York in 1998 and completed his postdoctoral training at Harvard University in 2001. Then, he served the Department of Veterans Affairs of the United States as a principal investigator (2002–2016), in affiliation with the School of Medicine, University of California, in Irvine. Currently, he is a professor at Baotou Medical College, Inner Mongolia University of Science and Technology. He has published dozens of research articles on various subjects including zoology, cardiovascular biology, gastroenterology, and cancer biology. He holds membership with the AGA, AHA, ASBMB, and several other organizations and also serves on the editorial board of multiple professional journals and serves as a solicited reviewer for national and international funding agencies.

Contents

Preface

The word *esophagus* (or oesophagus) derives from twoGreek words, *eosin* and *phagos,* meaning to carry and eat. Now itrefers to the tubular structure between thepharynxand thestomach. It begins at the back of the mouth, goes down behind the mediastinum, passes through the diaphragm, and ends into the stomach. There is a muscular ring at each end, known as the upper esophageal sphincter and the lower esophageal sphincter, respectively, which controls what gets in and what gets out. With the aid from peristaltic contractions, this pipe sendsfood to a long journey of digestion.

We open this book with the chapter "Anatomy of the Esophagus," written by Dr. Fehatoglu and Dr. Kivilcim (Okan University, Turkey), because we think it is absolutely essential to have such knowledge before getting into the rest of the book.

In human adults, the esophagus is about 25 cm in length, with a wall consisting of the mucosa, the submucosa, the muscularis propria, and an outer layer of connective tissue called the adventitia. The mucosa is astratified squamous epithelium composed of three layers of squamous cells, which can be easily distinguished from thesingle layer of columnar cellsof the stomach at the gastroesophageal junction. Unlike in other animals, the human esophageal epithelium is not covered with keratin, because it needs to turn over rapidly to minimize the abrasive effects of food. Within the esophageal wall, there are glands producing mucus to facilitate food passing through.

When food is being swallowed, the upper sphincter relaxes, allowing food to enter the pipe. Peristaltic contractions of the esophageal muscle push the food down through the lower sphincter into the stomach. The lower esophageal sphincter is like a dam sitting in between the esophagus and the stomach to prevent the stomach contents to back up into the esophagus. When this muscular structure does not hold well, gastroesophageal reflux disease (GERD) takes place, in which case stomach acid mixed with duodenal content gets into the esophagus. If this happens frequently and substantially enough, it can lead to esophagitis and then to Barrett's esophagus, a premalignant metaplasia of the esophageal lining changing from stratified squamous epithelium to simple columnar epithelium. Compared to normal people, individuals with Barrett's esophagus can have as high as 400-fold increased risk to develop esophageal cancer.

Esophageal cancer is globally ranked as number nine by its prevalence and number six by its mortality. Therefore, we dedicate the next five chapters of the book to this deadliest disease. There are two types of esophageal cancer commonly seen. Esophageal squamous cell carcinoma (ESCC) is the predominant one, accounting for 90–95% of all cases of esophageal cancer. It occurs in the squamous cell lining of the middle section of the esophagus and is more often found in Asia and Africa. China alone is responsible for more than 50% of the patient population. Esophageal adenocarcinoma (EAC), on the other hand, takes place in the cuboidal cells of the esophageal glands near the gastroesophageal junction and has been growing rapidly in western countries in recent years. We start this section with an overall commentary, written by Romanian scholars, on current treatment options for esophageal cancer, including chemotherapy, radiotherapy, resection surgery, and minimally invasive approach, followed by two chapters, contributed by Dr. Calduch et al. (Hospital Clinic University of Valencia, Spain) and Dr. Buruzovic et al. (Harvard Medical School, USA), which go into more details about minimally invasive surgery and radiotherapy, respectively. There is a bundle of evidence showing that minimally invasive surgery is a more favorable approach to treat cancer in contrast to open surgery, and a combination of external beam radiation therapy and moderate-dose rate brachytherapy can achieve a better outcome.

The progress of esophageal cancer is staged based on metastasis, i.e., how far the cancer cells have invaded into the esophageal wall or other organs, how many lymph nodes are affected, etc. Chapter 5, written by Dr. Makino et al. (Nippon Medical School, Japan), demonstrates how lymph node dissection is performed as a part of the treatment for esophageal cancer. They explain the technical differences in ESCC versus EAC so clearly that a professional reader would not have much difficulty to perform the surgery on his own just using the chapter as a reference.

Because of the critical location of the esophagus, any abnormalities associated with this organ can seriously obstruct food uptake and thereby impair the nutritional balance of the individual. For esophageal cancer patients, this is particularly devastating because either chemo-radiotherapy or surgical treatment can cause severe damage to the already problematic organ. Chapter 6 from Dr. Schizas and his associates (National and Kapodistrian University of Athens, Greece) has a long discussion on this topic and provides clear guidelines for nutritional management in different situations, including dietary counseling, oral supplementation, tube feeding, and combination of all.

Besides cancer, the other common abnormalities associated with the esophagus include esophagitis, varices,constrictions, motility disorders, as well as congenital diseases like atresia, trachea-esophageal fistula, achalasia, and diverticula. In the next chapter, Dr. Hosseinpour and Dr. Ahmadi (Isfahan University of Medical Sciences, Iran) present a full description on these birth defects, based on their years of experience in the pediatric world. Esophageal atresia refers to the situations in which esophageal tube closes itself before reaching the stomach. So, whatever eaten or drunk cannot get into the rest of the digestive system. It happens in 1 in about 2500 newborns. Trachea-esophageal fistula, on the other hand, refers to a condition in which the esophageal tube accidentally hooks up with the trachea; as a result, whatever eaten or drunk goes into the respiratory system. These two events could take place together or separately. The common treatment is surgically separating the esophagus from the trachea and reconnecting the esophagus to the stomach. Esophageal achalasia is not a connection problem, rather a case of muscular malfunction in which the lower esophageal sphincter is constantly closed so that whatever eaten or drunk remains in the esophagus and, consequently, the esophagus becomes massively stretched and acts like a “pseudo-stomach.” Besides surgical treatment, agents like calcium channel blockers can be used to relax the sphincter. However, while achalasia is relieved, GERD could step in to take the place because after such medication, the lower sphincter would not be able to hold the stomach acid below the esophagus. Fortunately, this is a rare disease, only happens in 1 per 100,000 people. Esophageal diverticulum occurs in response to inflammation or high internal pressure. A protruding pouch forms from the side of the esophageal wall. Surgical treatment is usually the way of management.

GERD is largely associated with the fast-growing obese/overweight population. The excess fat in the abdominal area puts a constant pressure on the stomach and creates a high frequency of esophageal acid exposure. A recent study showed that global obesity rates have doubled since 1980. It is predicted that by the year 2020, 77.6% of American men and 71.1% of American women will be overweight. A similar trend is also seen in China, the most populated state. According to the statistics in 2013, at least 46 million of Chinese adults were suffering from obesity, and another 300 million were considered as overweight. Current GERD treatment primarily relies on acid-suppressive medications (i.e., proton pump inhibitors or PPI) and repair surgery, but neither is a clear winner thus far. In fact, increasing evidence shows multiple side effects associated with this line of drugs, such as decreased absorption of vitamins/minerals, susceptibility to infections, bone fracture, and even elevated risk of developing cancer. For these reasons, the Food and Drug Administration of the United States has repeatedly issued warnings on the use of PPI. For people who have responded to medication but continue to experience GERD symptoms, surgery to reconstruct the esophageal sphincter is usually an option. However, only 5% of GERD patients undergo surgery, and follow-up study found that almost two-thirds of the surgery patients were back on medication. In Chapter 8, Tunisian scholars present a retrospective study on PPI use in elderly people, raising alert on these drugs despite their effectiveness in control of GERD symptoms.

There is an old Chinese saying, "All diseases come from the mouth." In modern civilization, this may not be absolutely true, but it tells how important eating/drinking is to our health. The next chapter (Larrosa-Haro and Sanchez-Ramirez, Mexico) has a discussion on the issue of caustic ingestion in underaged population. In developing and underdeveloped countries, this happens more often than we think, and it demands attention from both parents and the health professionals. Finally, we close this section with a rare topic called lymphocytic esophagitis, contributed by Dr. Daoud and Dr. Bouin (University of Montreal, Canada), which is not yet considered as a disease because the esophagus looks perfectly normal under the endoscope. However, patients experience discomfort in the chest as well as dysphagia, and histological examination reveals accumulation of peripapillary lymphocytic infiltrate within esophageal mucosa. Although "it is a condition in search of a disease" at this point, this topic demands a more vigorous study.

The human body is like a machine, and when it has a problem, health professionals like engineers will step in to fix it. However, all living organisms, including humans, age, and various diseases and other incidences will consume our bodies till a point where they are unrepairable, and then we die. This has made a lot of people think of alternatives. Some engineers with adequate knowledge of bioscience started to think of a possibility of using nonbiological materials to replace those sick or unrepairable organs. Then a new discipline was born, i.e., tissue engineering. In our last chapter of the book, professor Zhu and his team (Ningbo University, China) introduce some recent progress in this field, particularly about esophageal engineering. It is exciting to learn that in the near future, we could have some parts in our body that can never get sick.

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Section 1

Anatomy of the Esophagus

Chapter 1

Anatomy of Esophagus

Murat Ferhat Ferhatoglu and Taner Kıvılcım

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69583

Abstract

Anatomy knowledge is the basic stone of healing diseases. Arteries, veins, wall structure, nerves, narrowing, curves, relations with other organs are very important to understand esophagial diseases. In this chapter we aimed to explain anatomical fundementals of oesophagus.

Keywords: anatomy, esophagus, parts of esophagus, blood supply of esophagus, innervation of esophagus

1. Introduction

Esophagus is a muscular tube-like organ that originates from endodermal primitive gut, 25–28 cm long, approximately 2 cm in diameter, located between lower border of laryngeal part of pharynx (**Figure 1**) and cardia of stomach. Start and end points of esophagus correspond to 6th cervical vertebra and 11th thoracic vertebra topographically, and the gastroesophageal junction corresponds to xiphoid process of sternum. Five cm of esophagus is in the neck, and it descends over superior mediastinum and posterior mediastinum approximately 17–18 cm, continues for 1–1.5 cm in diaphragm, ending with 2–3 cm of esophagus in abdomen (**Figure 2**) [1, 2]. Sex, age, physical condition, and gender affect the length of esophagus. A newborn's esophagus is 18 cm long, and it begins and ends one or two vertebra higher than in adult. Esophagus lengthens to 22 cm long by age 3 years and to 27 cm by age 10 years [3, 4].

2. Structure of esophagus

Esophagus consists of four histologic layers: mucosa, submucosa, muscularis propia, and adventitia.

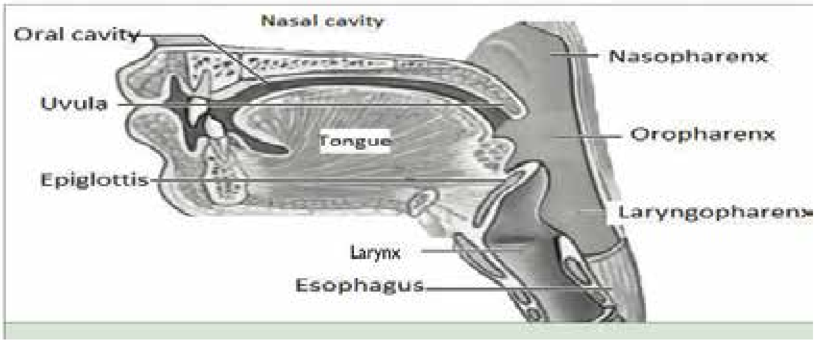

Figure 1. Anatomy of larynx (with permission of Turkish Surgery Association).

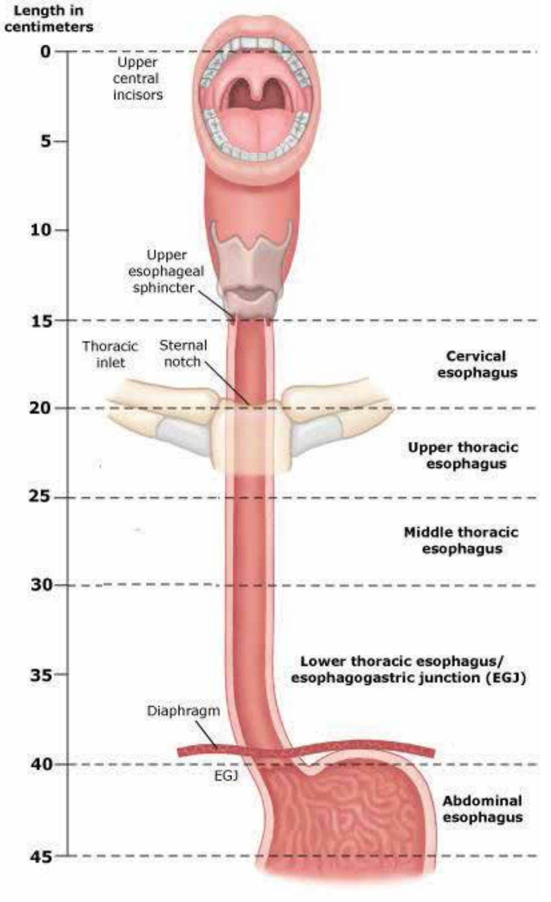

Figure 2. Length of esophageal parts.

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2.1. Mucosa

Nonkeratinized stratified squamous epithelium covers all esophageal lumen. Lamina propia and lamina muscularis mucosa are located under this epithelium. Lamina propia consists mostly of loose connective tissue and lamina muscularis mucosa consists of some smooth muscle tissue and elastic fibers. Nonkeratinized stratified squamous epithelium of mucosa transforms simple columnar epithelium in cardia of stomach, occurring at a point called "Z line," an irregular zigzag line. On endoscopy, esophageal mucosa is paler than mucosa of stomach.

2.2. Submucosa

This layer consists of elastic and collagen fibers that form a dense, irregular connective tissue. This layer consists of veins, lymphatics, and meissner plexus.

2.3. Muscularis propia

Both longitudinal and circular muscles form tube-like esophagus: longitudinal muscle fibers are located superficially and the circular muscle fibers are located deeply. Longitudinal fibers begin from posterior face of cricoid cartilage and form a triangle named as "Lamier triangle," which is limited by longitudinal muscle fibers laterally and cricopharyngeus muscle superiorly. Another triangle, called "Killian triangle," is found in this area, and borders of this triangle are formed by inferior constrictor muscle of pharynx and cricopharyngeus muscle. These weaker areas are important for the formation of Zencker's diverticula. Longitudinal muscle fibers are gathered laterally in upper portion of esophagus, but these fibers expand and surround all surfaces at lower sides, becoming strongest in lower third part of esophagus. Circular muscle fibers are located under longitudinal muscle, and the circular muscle is thinner than longitudinal muscle. Circular muscles are not actually circular at all parts of esophagus; these fibers are more elliptic in upper third part and become more circular at lower third part of esophagus. Circular muscle fibers do not make a regular formation, but run in an irregular pattern making a shutter-like system. Spontaneous perforation of esophagus usually occurs in last 2 cm, and this perforation consists of entire esophageal wall, causing mediastinitis because of gastric acid leakage. Upper part of esophagus consists of striated muscle and the lower part consists of smooth muscle fibers. Transition zone differs in all humans, but mostly upper quarter consists only of striated muscle fibers; second quarter consists of both striated and smooth muscle fibers; and lower half consists of only smooth muscle fibers (Aurbach plexus is in this layer).

2.4. Adventitia

This layer surrounds most of the esophagus and consists of loose connective tissue. Because no serosa is found on esophagus, infections, and tumors can spread easily [5, 6].

3. Narrowings and curves of esophagus

Esophagus has seven narrowing points that can be seen using esophagoscopy or barium passage graphy. Four classic narrowings are found in almost all people; three other narrowings are found in certain medical conditions.

First classical narrowing is at the beginning point, and oropharyngeal muscle forms it; this part is the second narrowest point after orifice of appendix vermiformis in alimentary tract. This first narrowing point's luminal diameter is approximately 1.4–1.5 cm, and it is located 15 cm after maxillary central incisor teeth. Topographically, this first point corresponds to corpus of 6th cervical vertebra. This narrowing is named "upper esophageal sphincter." Second narrowing corresponds to plane that is located at superior border of sternum. Anterior and posterior esophageal walls become closer in hyperflexion, and this partial narrowing point occurs. Third narrowing is one of classical narrowings made by aortic arch. This point corresponds to 4th thoracic vertebra topographically and measures 1.5–1.6 cm in width. Point is located 22.5 cm after maxillary central incisor teeth, 7 cm below cricopharyngeus muscle [2]. Fourth narrowing (third classical narrowing) is located at crossing point of esophagus and left main bronchium. This point is located at level of 5th dorsal vertebra, and 27.5 cm after maxillary central incisor teeth and 9 cm below oropharyngeal muscle. Fifth narrowing point is formed if patient has atrial dilatation caused by mitral stenosis. This point is located just below bronchial narrowing. Sixth narrowing, called "Laimer narrowing," is located at second crossing point of esophagus and aorta. This point is located at plane corresponding to upper edge of 10th dorsal vertebral corpus. Laimer narrowing occurs in situation of aortic atherosclerosis. Just above this narrowing, a partial dilatation called "epiphrenic ampulla" or "Vorgamen de Luschka" is found. Last narrowing (and 4th classical narrowing) is made by esophageal hiatus that originates from right crus of diaphragm, and is located at the level of 11th dorsal vertebra and 40 cm after maxillary central incisor teeth; it is 1–1.5 cm in length and1.5–1.8 cm in width. This last narrowing is named "lower esophageal sphincter." Lower sphincter consists of a physiological sphincter mechanism made by muscle fibers of right crus of diaphragm; it provides an antireflux mechanism. When a person is not eating, esophageal lumen is closed above lower esophageal sphincter. Esophagus is primarily median and vertical, but has three slight curves located in neck, behind left bronchus, and at bifurcation of trachea (**Picture 1**).

Esophagus is located at left of midline at level of 1st dorsal vertebra, right of midline at level of 6th dorsal vertebra, and left of midline again at level of 10th dorsal vertebra. Thus, esophagus makes a reverse "S" all the way in front of vertebral column. These narrowings and curves are important landmarks for radiological and endoscopic investigation of abnormalities, cancer diagnosis, and stricture formation after swallowing of chemicals [2, 7].

Esophagus is anatomically divided into three parts: cervical esophagus, thoracic esophagus, and abdominal esophagus.

3.1. Cervical esophagus

Cervical esophagus starts at inferior margin of cricoid cartilage that corresponds to corpus of 6th cervical vertebra. This level is marked by a carotid tubercula named "Chasseing tubercula,"

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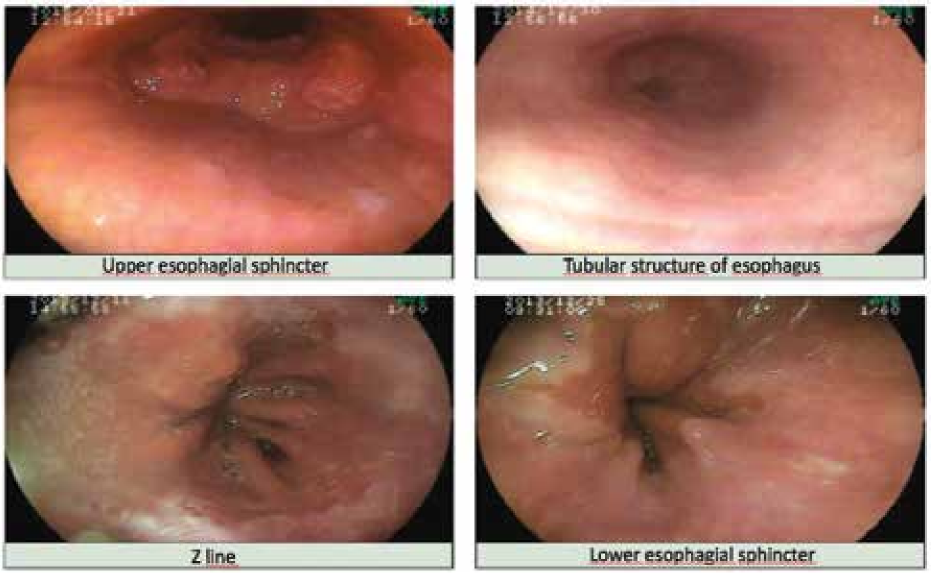

Picture 1. Endoscopic view of esophagus (with the permission of Turkish Surgery Association).

which is an important landmark in cervical esophagectomy. Cervical esophagus ends at inferior edge of first dorsal vertebra that comes up to a horizontal plane of jugular incisura of sternum. The endpoint is the starting point of upper mediastinum, and from this point it is thoracic esophagus. Cervical esophagus is 5–6 cm long, and its luminal diameter is 1.4–1.5 cm at its narrowest point.

3.1.1. Surrounding structures

Esophagus runs in deepest fascial plane of neck, leaning between trachea anteriorly and vertebra posteriorly. Esophagus is attached to prevertebral fascia by sagittal septa, which forms retropharyngeal and retro-esophagial spaces.

Esophagus is covered by larynx and trachea anteriorly (**Figure 3**), but this covering is partial, and an open margin is found on left anterior side, which provides natural surgical access. Esophagus attaches with tracheoesophageal muscle fibers to trachea; it is easy to separate tracheoesophageal plane, except in pathological circumstances. Esophagus's closest structure is carotid artery anterolaterally, which lies 1–2 cm away from it. Inferior thyroid artery, thyroid lobes, and recurrent laryngeal nerves are other important contiguities of esophagus, and ductus thoracicus lies on left side of it. Esophagus connects prevertebral muscles, cervical vertebras, and prevertebral laminas posteriorly. Thoracic duct connects to left "Pirogoff angle," and it makes a slight connection to left side of esophagus.

3.1.2. Importance of surrounding structures

Sagittal septa, which forms retropharyngeal and retro-esophagial spaces, blocks the diffusion of abscess of this area to upper mediastinum, but abscess can diffuse via pretracheal space to the upper mediastinum and can cause a fatal complication. Pretracheal space is important in that it can be perforated, primarily during an esophagectomy.

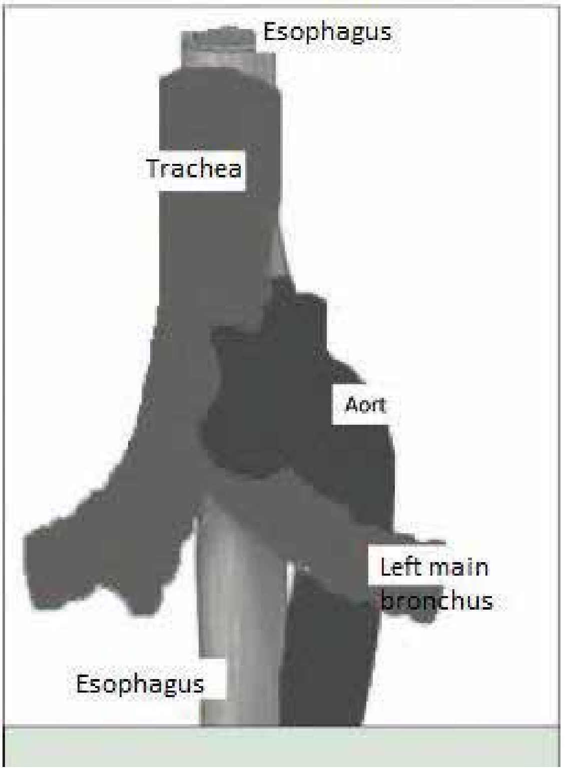

Figure 3. Placement of esophagus relative to other anatomic structures (with permission of Turkish Surgery Association).

Recurrent laryngeal nerve (RLN) lies in tracheoesophageal sulcus, and esophagus is close to this nerve, which is important in case of cervical esophagectomy. Injury of RLN causes unilateral difficulty in swallowing and hoarseness; bilateral injury causes closure of vocal cords in median position, and a tracheostomy becomes necessary. Especially on left side of esophagus, RLN is so close to esophagus that it is easy to injure a nerve with a careless dissection. Thus, dissection should be made close to esophageal muscle fibers to avoid this complication. As previously mentioned, thoracic duct connects to left Pirogoff angle, and it makes a slight connection to left side of esophagus. To avoid harm to thoracic duct, a careful dissection should be made, especially in cervical esophagectomy [8, 9].

3.2. Thoracic esophagus

Measuring 16–18 cm in length, thoracic esophagus is in upper and posterior mediastinum. Running from 1st to 11th dorsal vertebra, it does not fit concavity of vertebral column. However, it changes location to left gradually from start to end. At beginning, it is located between vertebral column and trachea, slightly left of midline and 5 cm left of vertebral column at level of diaphragmatic hiatus (**Figure 4**). Parietal sheet of pleura is tightly connected to both sides of vertebral column, and these connections cause esophageal-pleural recesses that make dissection of esophagus in thorax more difficult. Thus, if a pleural rupture occurs in this area during surgery, fixing rupture can present a challenge for surgeon [2].

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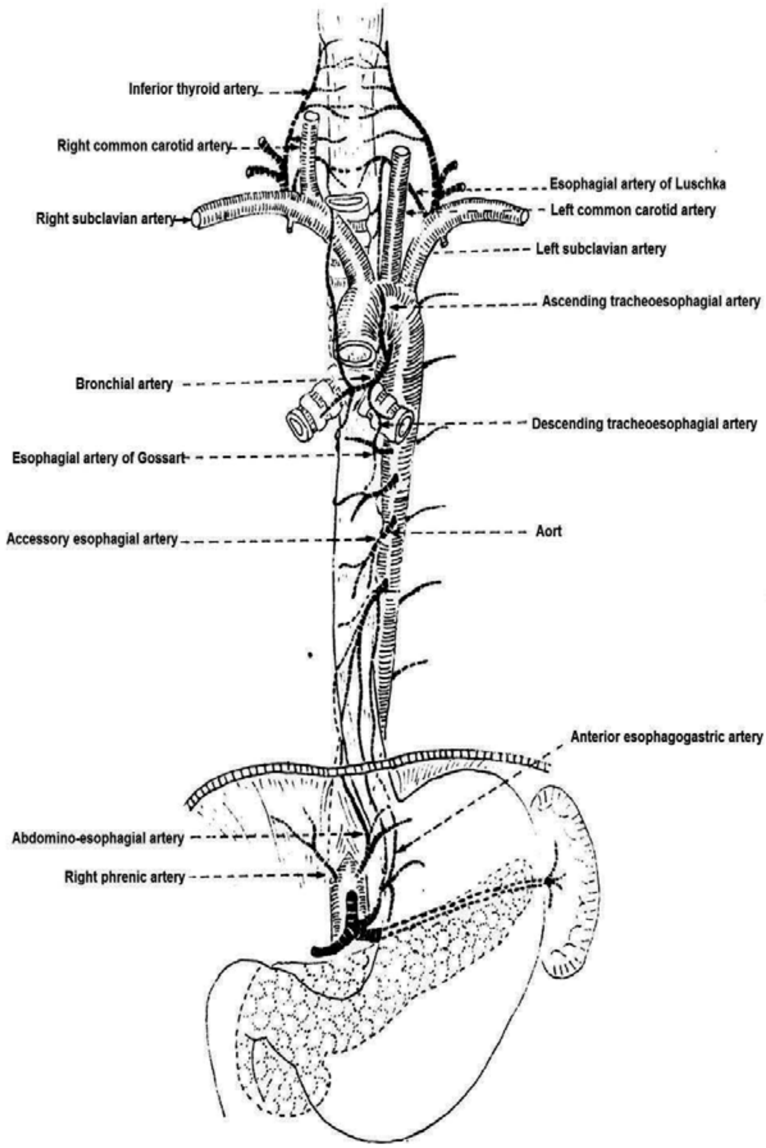

Figure 4. Arteries of Esophagus.

As previously discussed, esophagus within thoracic cavity contains three classical narrowings, two conditional narrowings, and two curves.

3.2.1. Surrounding structures

Most important and challenging structure in this region is thoracic duct, which lies behind esophagus throughout thorax. Thoracic duct is located slightly apart from esophagus in inferior third part of thorax, but it comes closer as esophagus goes upward. Trachea, aortic arch, right pulmonary artery, left main bronchus, plexus of esophagus, pericardium, left atrium, and anterior vagus nerve are found anterior to esophagus. At posterior side, esophagus connects to vertebral column, longus colli muscle, posterior intercostal arteries, azygos vein, hemiazygos vein, anterior wall of aorta, posterior vagal nerve, and pleura. Aortic arch, left subclavian artery, left inferior laryngeal nerve, left vagus nerve, thoracic ductus, and thoracic part of aorta are located on left side of esophagus. Azygos vein, pleura of mediastinum, right main bronchus, and right vagus nerve are located on right side.

3.2.2. Importance of surrounding structures

Close proximity of upper two-thirds of esophagus to thoracic duct increases risk of thoracic duct injury in middle and upper mediastinal dissection of esophagus; thus, careful dissection should be performed in this area.

At a level of diaphragmatic hiatus, a soft areolar tissue connects esophagus to diaphragmatic cruses, and a slight concave area called "portal concavity" allows formation of a hiatal hernia.

The area between aortic arch and esophagus is comprised of aorticoesophagial muscle fibers that include large vessels; dissection of this area is fairly simple, except in the case of tumor invasion. If tumoral invasion occurs among these large vessels, removal is challenging and dangerous.

Upper mediastinum becomes narrower above aortic arch, and esophageal tumors can easily infiltrate left recurrent laryngeal nerve and respiratory system; however, aortic arch and azygos vein block tumors in these areas to infiltrate lower parts of mediastinum.

Lower parts of thoracic esophagus are surrounded by soft areolar tissue. Here esophagus is not touching adjacent organs and descends slightly away from the vertebral column, making dissection and resection easier and tumor infiltration more difficult in this area.

Two weak areas in esophagus that can be vulnerable to pulsing diverticula are upper and lower parts of a cricoid muscle. In addition, another weak area is located on left posterior esophageal wall, very close to diaphragmatic hiatus, spontaneous rupture of esophagus can occur [2, 10].

3.3. Abdominal esophagus

Abdominal esophagus is 1–2.5 cm long and is topographically located at 11thvertebral plane posteriorly. The plane passes through 7th rib cartilage and sternum anteriorly. It passes through esophageal hiatus of diaphragm, which is comprised of muscular fibers of right crus. The anterior side is longer than posterior side of esophagus because diaphragmatic crura are oblique. Anterior and lateral sides are partially covered by visceral peritoneum, and posterior side is nonperitoneal side. Three ligaments connect esophagus to spleen, liver, and diaphragm. They are hepatogastric ligament, gastrosplenic ligament, and gastrophrenic ligament.

3.3.1. Surrounding structures

Following structures are located near abdominal esophagus: posterior side segment of two-thirds of liver, left vagus nerve and esophageal plexus anteriorly, left and right crus of diaphragm, aorta and left inferior phrenic artery posteriorly, caudate lobe of liver at the right side, and fundus of stomach at left side.

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Esophageal hiatus is located on right side of midline and is 2 cm in diameter. Topographically, it is located at 10th vertebral plane. Before reaching hiatus, esophagus dilatates at a place called "epithetic ampulla" that is delaying point of morsel when swallowing during radiologic examinations.

Esophagus ends at a place called "cardia of stomach." Right side of esophagus continues as lesser curvate of stomach, and left side angles with greater curvate of stomach, forming "angle of Hiss." A mucosal tongue that descends into stomach is called "Gubaroff valvula." Hiss angle and Gubaroff valvula are important in antireflux mechanism [11].

Phrenoeosophagial ligament is primary part of antireflux mechanism that includes Gubaroff valvula and angle of Hiss (**Figure 5**). This ligament consists of subpleural fascia, pleura,

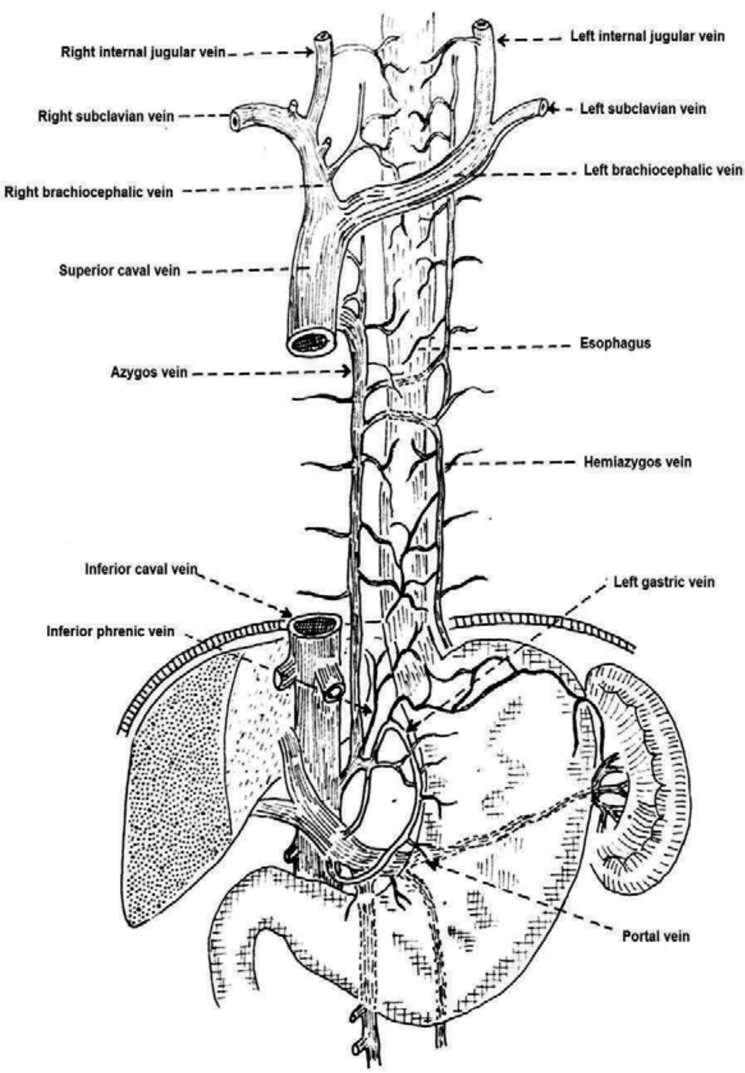

Figure 5. Veins of Esophagus.

phrenoesophageal fascia, and transverse fascia of abdomen and peritoneum. Fibers of this ligament that reach upward are called "Juvara fibers"; downward fibers are called "Rouget fibers." Phrenoesophageal ligament resists vigorous abdominal pressure that pushes stomach to intrathoracic cavity, but it allows esophagus to move upward and downward while swallowing. This ligament makes gastroesophageal junction both flexible and tight [12, 13].

4. Connections that stabilize esophagus

Fibrotic membrane that attaches esophagus to vertebral column is called "Bouteiller membrane." This membrane is tight over diaphragmatic hiatus and limits extreme movements of esophagus. However, under hiatus, membrane is loose and long. Phrenogastric ligament lies between diaphragm and cardia of stomach and both vagus nerves. Vagus nerves hang esophagus to thoracic cavity; thus, cutting vagus nerves elongates esophagus 4–5 cm [2].

4.1. Arteries of esophagus

Inferior thyroid artery provides primary arterial flow to the cervical esophagus, and subclavian artery, main carotid artery, vertebral arteries, ascendant pharyngeal artery, superficial cervical artery, and costocervical trunk are other arterial blood flow providers to cervical esophagus. Thoracic portion of esophagus takes blood flow from aorta, bronchial arteries, and right intercostal arteries. The abdominal esophagus is fed by left gastric artery, short gastric arteries, and descending branch of left phrenic artery. Inferior thyroid artery supplies arterial blood flow to cervical portion of esophagus (**Figure 6**). An excessively low resection of cervical esophagus causes devascularization to this area. In addition, aggressive resection and mobilization or laceration of bronchial artery, or cutting recurrent branches of left gastric artery and inferior phrenic artery causes devascularization at level of tracheal carina. Esophageal arterial blood flow is extremely rich and adequate for anastomosis, but a poor blood supply or careless or over aggressive dissection can cause anastomotic leakage in esophagus [14–16].

4.2. Veins of esophagus

Venous system of esophagus begins at submucosal plexus, which perforates muscular layer and empties into azygos system. Cervical portions of venous drainage empty into inferior thyroid veins. Thoracic portion's venous drainage empties into azygos vein, right brachiocephalic vein and, rarely, vertebral veins on right side, and hemiazygos vein, left brachiocephalic vein and, rarely, vertebral veins on left side. Venous drainage of abdominal portions empties primarily into left gastric veins. Other veins that drain esophageal venous plexus are short gastric veins, splenic vein, left gastroepiploic vein, and branches of an inferior phrenic vein. Lower esophageal veins connect to superior caval venous system by azygos and hemiazygos veins with multiple shunts, and other multiple shunts are located between inferior caval system and lower esophagus (**Figure 7**). Retrograde flow of esophageal venous system causes venous dilatation and varices, and these varices can cause fatal bleeding [2, 14, 17].

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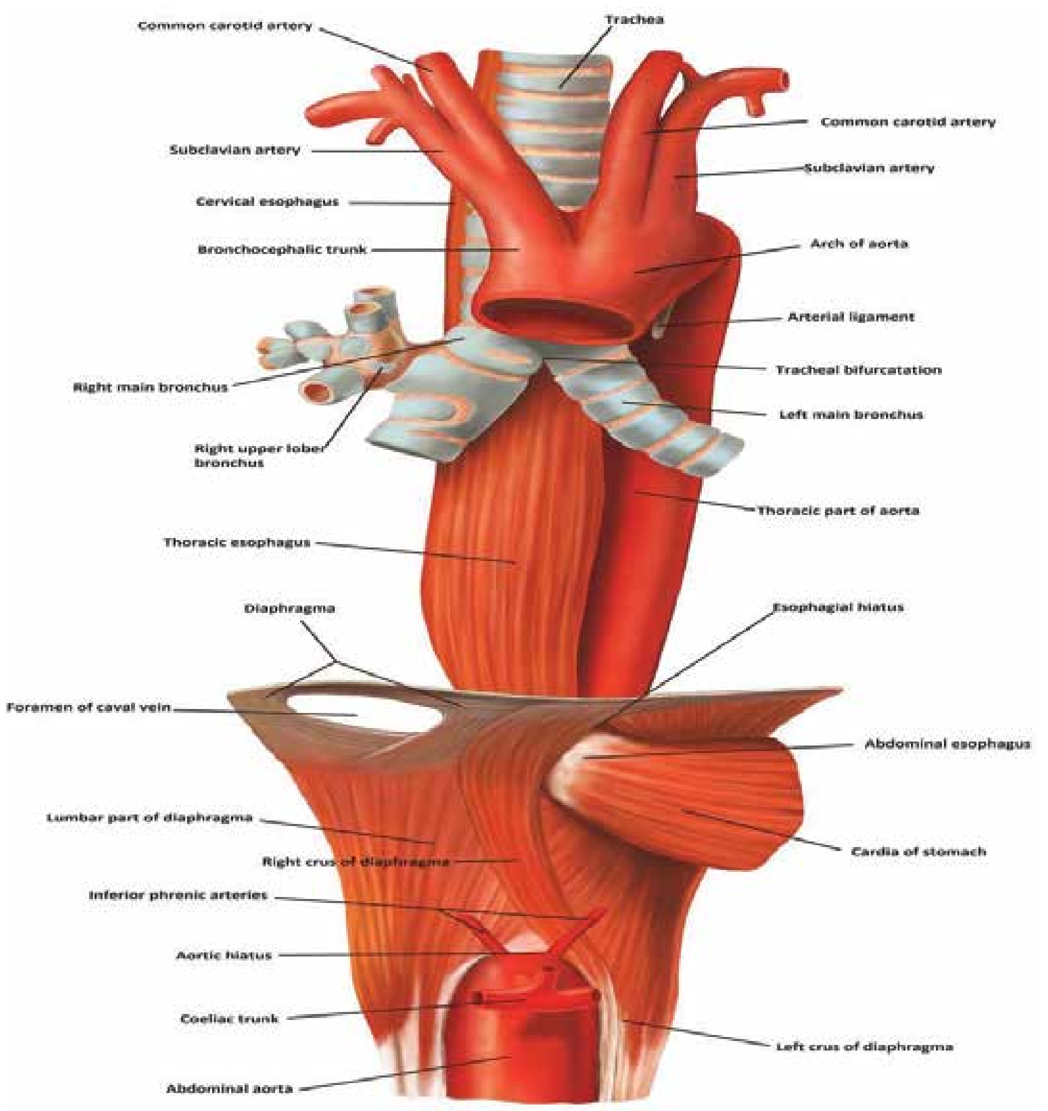

Figure 6. Relation among esophagus, diaphragm, and aorta (with permission from Turkish Surgery Association).

4.3. Lymphatics of esophagus

Lymphatics are located in every layer of esophagus, but primarily at lamina propria, forming a giant network system. Cervical lymphatics empty internal jugular lymph nodes and upper tracheal lymph nodes. An internal jugular lymphatic system that forms deeper cervical lymphatic system connects with lymphatic duct at right side and thoracic duct at left side.

Lymphatics of thoracic esophagus empty posterior parietal, diaphragmatic, tracheal, tracheobronchial, retrocardiac, and infracardiac lymph nodes.

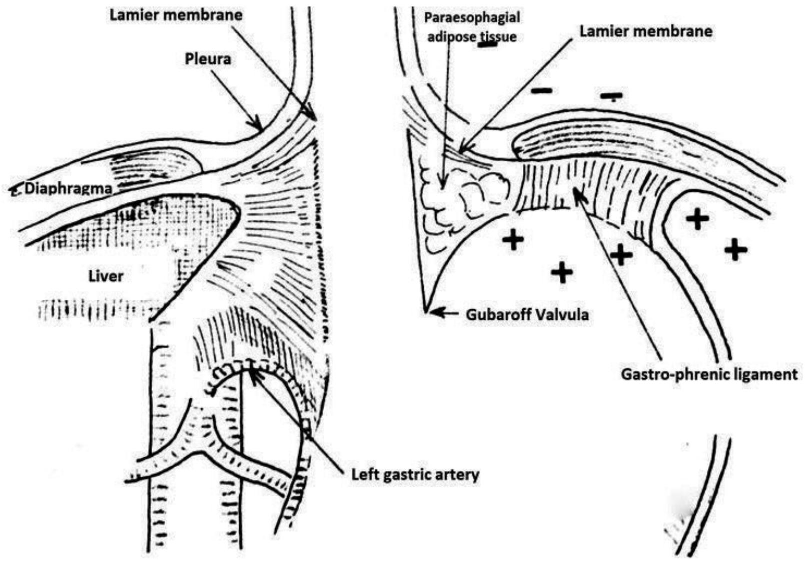

Figure 7. Anti-reflux mechanism of esophagus.

Abdominal parts of lymphatic system empty left gastric, paracardiac lymph nodes, and all these nodes connect to coeliac lymph nodes. Coeliac lymph nodes empty cisterna chyli or thoracic duct.

Posterior parietal lymph nodes include posterior mediastinal and intercostal lymph nodes and connect with thoracic duct or right lymphatic duct. Only posterior part of diaphragmatic lymph nodes are connected to esophageal lymphatic system, and these lymph nodes empty to posterior parietal lymph nodes.

Tracheal or paratracheal lymph nodes are located on two sides of trachea, and tracheobronchial lymph nodes are located around bifurcation of trachea. Tuberculosis, which causes necrosis and fibrosis of tracheobronchial lymph nodes, forms traction diverticula of esophagus. These two lymphatic systems form a broch mediastinal lymphatic chain that empties to thoracic duct or right lymphatic duct (**Figure 8**) [18, 19].

4.4. Innervation of esophagus:

Parasympathetic and sympathetic nerves form esophageal innervation, carrying stimuli to esophageal muscles, glands, veins, and arteries.

4.4.1. Parasymphatic innervation

Parasympathatic fibers that innervate pharynx and upper part of esophagus come from ambiguous nuclei of brain. Esophageal innervation is primarily accomplished by vagus nerves, which end at dorsal vagal nuclei of brain. Cervical esophagus takes thin fibers from both recurrent laryngeal nerves. Both left and right recurrent laryngeal nerves arise from vagus nerves, but on left side, a recurrent laryngeal nerve is closer to aortic arch. On right side,

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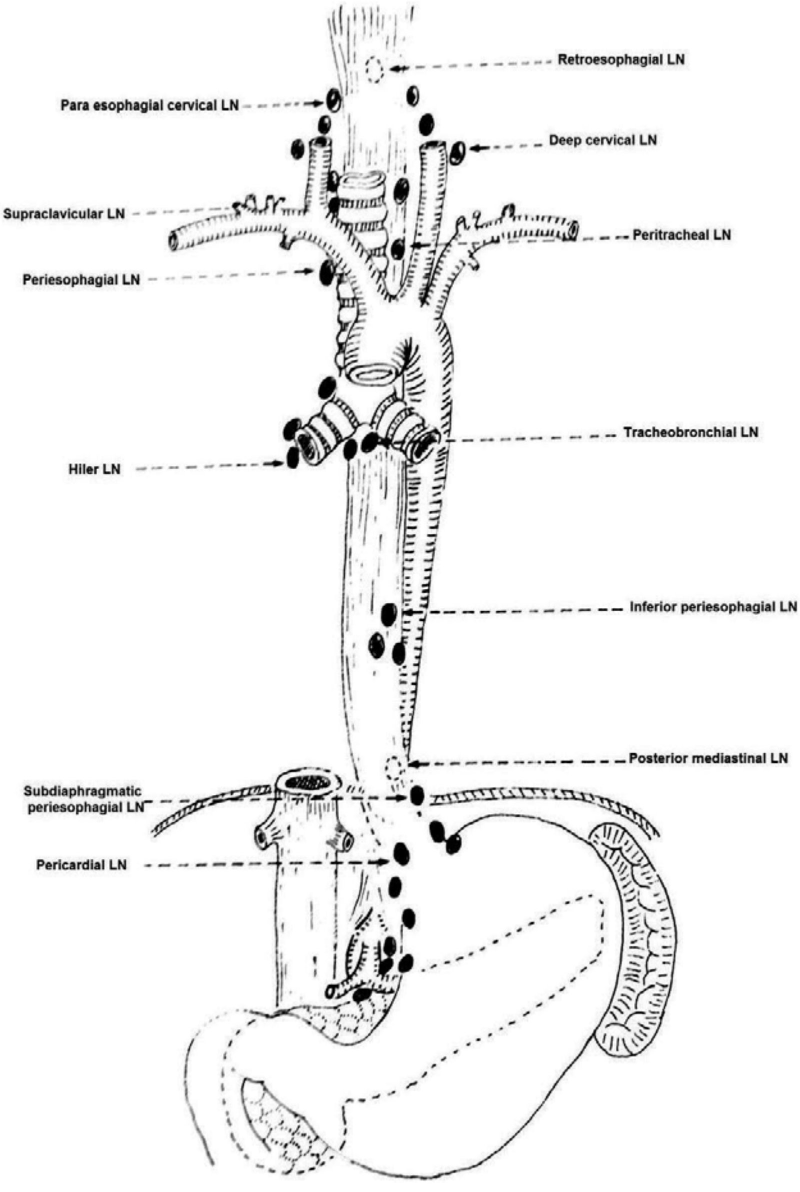

Figure 8. Lymphatics of esophagus.

it is closer to subclavian artery. Finally, left and right recurrent laryngeal nerves run in sulcus between trachea and esophagus. The thoracic esophagus is primarily innervated by vagus nerves, but the upper part of thoracic esophagus takes some fibers from left recurrent laryngeal nerve. Vagus nerve fibers form two to four branches under tracheal bifurcation, and these nerve branches are located on anterior face of esophagus at level of posterior mediastinum. Near esophageal hiatus, these nerve branches unite and form two vagal trunks of esophagus.

Variation of vagal trunks is important during vagotomy. A surgeon should be aware of these variations and be careful because more than one branch can be found in anterior or posterior vagal trunk or both.

4.4.2. Sympathetic innervation

The upper part of esophagus is innervated by pharyngeal plexus, which is fed by upper cervical ganglions, middle cervical ganglions, and sympathetic trunks of vertebral ganglions while running downward. Superior parts of the thoracic esophagus are innervated by stellate ganglion and subclavian ansa. Lower parts of thoracic esophagus are innervated by greater splanchnic nerves that end at coeliac plexus. Left greater splanchnic nerve and right inferior phrenic nerve innervate abdominal esophagus [20, 21].

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Section 2

Esophageal Cancer

Multimodal Treatment for Cancer of the Esophagus

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.70991

Abstract

There are about 500,000 new cases of cancer of the esophagus and 400,000 esophageal cancer-related deaths recorded annually around the world. The disease is three to four times more frequent in men than in women, being the sixth most common cancer and the fifth most frequent cancer-related death among men. The prognosis of esophageal cancer is quite poor, despite advances in surgical procedures (two-field and three-field lymph node dissection) and perioperative management, which is still controversial. The use of chemotherapy and radiotherapy in combination with surgery might be a new approach for future treatment. Progress in optical technology has led to the development of a new minimally invasive surgical approach for the treatment of esophageal cancer, namely esophagectomy.

Keywords: esophageal cancer, chemotherapy, surgery, radiotherapy, outcome

1. Introduction

There are about 500,000 new cases of cancer of the esophagus and 400,000 esophageal cancer-related deaths recorded annually around the world. The disease is three to four times more frequent in men than in women, being the sixth most common cancer and the fifth most frequent cancer-related death among men [1].

Even though esophageal cancer was not very common in Western populations, the incidence of esophageal adenocarcinoma and its related mortality have increased in the USA and certain European countries [2]. The incidence of adenocarcinomas involving the esophago-gastric junction, the distal esophagus and the gastric cardia has recorded a more significant increase [3]. The transition from squamous cell carcinoma to Barrett's metaplasia-associated adenocarcinoma in Western populations could have been determined by the increase in the incidence of obesity and obesity-induced reflux [4, 5].

There are two main subtypes of the disease, namely esophageal squamous cell carcinoma and esophageal adenocarcinoma. The most common causes of squamous cell carcinoma are tobacco and alcohol, and the most common causes of adenocarcinoma are tobacco, obesity and acid reflux [5]. There has been a major increase in the incidence of adenocarcinoma in North America and Europe, while squamous cell carcinoma is still the most common type of esophageal cancer in Asia [6].

The two subtypes of esophageal cancer have different clinical and biological characteristics. While squamous cell carcinomas occur in the middle or upper third of the esophagus, adenocarcinomas occur in the lower third of the esophagus. Abdominal lymph node metastasis is usually present in adenocarcinomas, and the incidence of cervical or upper mediastinal lymph node metastasis is more frequent in squamous cell carcinomas. Thus, the therapeutic approach is different for each subtype [7].

The prognosis of esophageal cancer is quite poor, despite advances in surgical procedures (two-field and three-field lymph node dissection) and perioperative management, which is still controversial [7]. The use of chemotherapy and radiotherapy in combination with surgery might be a new approach for future treatment. Progress in optical technology has led to the development of a new minimally invasive surgical approach for the treatment of esophageal cancer, namely esophagectomy. Long-term survival in resectable esophageal cancer is also influenced by definitive chemoradiotherapy [8]. Salvage esophagectomy is used in patients with esophageal cancer who were treated with chemoradiation as definitive therapy [9].

Although cancer of the esophagus is among the most common cancers in the world, there are few studies on this malignancy. There have been significant changes in the epidemiology of esophageal cancer in the past 30 years, with a striking increase in incidence in Western populations, where the number of adenocarcinomas has exceeded those of the squamous cell type [6]. On the other hand, squamous cell carcinoma is the most frequent subtype in Asian countries, mainly developing in the middle third of the esophagus, without any dramatic increase in the incidence of adenocarcinoma on this continent. New diagnostic, staging, and therapeutic options have improved survival rates for esophageal cancer.

Early stage adenocarcinoma of the esophagogastric junction (AEG) could be detected based on efficient screening for gastroesophageal reflux disease (GERD) and Barrett's metaplasia, which might be cured using endoscopic ablation or surgery [10].

The infection with *Helicobacter pylori* harboring the cagA gene seems to be associated with a reduced risk of esophageal adenocarcinoma [11, 12].

The potential role of COX-2 inhibitors in the effective chemoprevention of esophageal adenocarcinoma, characterized by COX-2 overexpression, is another aspect to be considered [13]. The types of surgery for cancer of the esophagus are divided based on the complex lymphatic drainage from the esophagus and gastric cardia and their anatomy.

http://dx.doi.org/10.5772/intechopen.70991

2. Esophageal resection

Hulscher et al. conducted a meta-analysis and obtained a 20% 5-year survival rate [14] following any of the two approaches. However, there were much higher rates of early morbidity and mortality in the case of transthoracic resection. On the other hand, in another study conducted by Hagen et al. [15], better survival rates (41% vs. 14%; $p < 0.001$) were obtained in 30 patients following en bloc esophagectomy compared with 39 patients undergoing transhiatal esophagectomy, suggesting the use of extended en bloc esophagectomy instead of transhiatal resection in the case of carcinoma of the lower third of the esophagus and gastric cardia [15].

Outcomes in esophageal cancer are often poor [16]. The best and most efficient surgical method in patients without evidence of spread to other parts of the body is the combination between esophagectomy and reconstruction surgery [7]. There are three more frequent minimally invasive techniques for esophagectomy: transhiatal esophagectomy, the Ivor Lewis esophagectomy (upper midline laparotomy combined with a right posterolateral thoracotomy), and the McKeown technique (right thoracotomy, upper midline laparotomy, and left neck incision). Several randomized trials compared transhiatal esophagectomy and standard transthoracic esophagectomy, showing no significant differences between them. The differences between transthoracic and transhiatal esophagectomy were examined in three randomized trials [17–21]. The results of these clinical trials showed no significant differences between the two approaches in what concerns patient survival. Hulscher et al. [22] conducted a randomized trial in patients with adenocarcinoma of the esophagus and gastric cardia (106 patients with transhiatal esophagectomy and 114 with transthoracic esophagectomy). There were lower morbidity rates in the case of transhiatal esophagectomy than in transthoracic esophagectomy with extended en bloc lymph node dissection. Despite the absence of statistically significant differences in terms of disease-free, median overall, and quality-adjusted survival, there was an improvement in long-term survival of patients with extended transthoracic resection. Asia, especially Japan, accounts for the majority of the more aggressive surgery records. Five-year survival rates following three-field lymph node dissection were 48.7% in a study conducted by Kato et al. [23] and 55.0% in a study by Akiyama et al. [24].

Esophagectomy can be either transhiatal or transthoracic, performed using the Ivor Lewis technique (combined laparotomy and right thoracotomy) and the modified McKeown procedure, involving laparotomy, right thoracotomy with neck anastomosis, left thoracotomy, or left thoracoabdominal incision [25]. The approach is chosen depending on tumor location and surgeon preferences. Good treatment outcomes result from the complexity of these surgical procedures, the experience of the surgeons, and intensive care resources [26].

A comprehensive randomized study assessing the differences between the transthoracic and the transhiatal approach indicated similar mortality rates for both procedures, whereas morbidity rates were lower for the transhiatal approach. The transthoracic group showed non-significant associations between this procedure and overall and disease-free survival. However, there was an improvement in locoregional disease-free survival following transthoracic esophagectomy in a subgroup of patients who did not present extensive nodal involvement [27].

Long-term survival rates following open esophagectomy do not differ significantly when comparing these surgical procedures, as shown by various meta-analyses and randomized trials [28]. In their study, Tabira et al. [29] recommended the use of three-field lymph node dissection in patients with one to four lymph node metastases. As indicated by Shiozaki et al. [30], neck dissection might be eliminated in patients with carcinoma in the middle or lower third of the esophagus without lymph node metastasis along the recurrent nerve chain. Lerut et al. [31] also proved an improvement in patient survival following three-field lymph node dissection.

When comparing three-field with two-field lymph node dissection for squamous cell carcinoma of the esophagus, Kato et al. obtained 5-year survival rates of 48.7% for the first approach and 33.7% for the second. However, this study was contested due to differences in patient characteristics. Isono et al. [32] conducted a nationwide study and obtained better survival rates when using three-field dissection instead of the two-field approach. Fujita et al. [33] also presented much better survival rates following three-field lymph node dissection ($p < 0.05$) for carcinoma in the upper or middle third of the esophagus spreading to the lymph nodes. Still, there were no differences in mortality, morbidity, and postoperative quality of life between the two approaches [33]. Radical esophagectomy helps remove ≥80 lymph nodes and 5-year survival rates are around 40–60% [34].

3. Minimally invasive surgery

Pulmonary complications after transthoracic esophagectomy are high. The minimally invasive thoracoscopic approach might result in lower morbidity and mortality rates. Being minimally invasive, thoracoscopy should replace the open approach. In a study conducted by Cuschieri et al. [35], the researchers performed right thoracoscopy (esophagectomy and lymph node dissection) in a small group of patients and paved the way for the future use of thoracoscopic esophagectomy. This procedure proved to be feasible and even superior to open surgery. Nevertheless, the first outcomes using this approach were not significantly better than those obtained with the open approach, mainly as a result of the great number of pulmonary complications [36–38]. However, a few medical research centers in Japan found a new stimulus. For example, Akaishi et al. [39] obtained good outcomes in 39 patients with cancer of the esophagus who underwent en bloc esophagectomy with radical lymph node dissection via right thoracoscopy, with the following parameters: 200±41 min operating time, 270±157 ml blood loss, and the number of harvested lymph nodes was 19.7±11. All patients survived and there was a modest decrease in vital capacity in 22 of them, without requiring postoperative ventilation. A significant finding of the study was that pulmonary complications were reduced compared with the open procedure.

In their study, Luketich et al. [40] proved that minimally invasive esophagectomy (MIE) is efficient and safe in the United States. The study was conducted on 1033 consecutive patients and results indicated a significantly lower mortality rate (0.9%), with an 8-day median hospital stay. In a study performed in the United Kingdom, Mamidanna et al. [41] assessed 7502 patients undergoing esophagectomy (E) and MIE ($n = 1.155$) and results showed no differences in terms of 30-day morbidity and mortality. MIE proved to be safe for use by professionals, without supplementary patient safety risks. Despite the low number of annual esophagectomies (2) per medical center, study results were similar and MIE was preferred in terms of perioperative outcomes. On the other hand, there are insufficient and incomplete cancer comparative research data. Certain centers noted higher lymph node retrieval following MIE with lymph node dissection [42–44], whereas others did not find any considerable differences [45]. In a study performed on 168 patients, Palazzo et al. [46] demonstrated that long-term survival was twice better in patients who underwent MIE (hazard ratio—2.0). Despite significant patient and tumor variables, there were concerns related to the ability to reproduce the major differences in results obtained for these groups. Additionally, the small number of patients might assign any variations to defective regulations.

In a study assessing three-field lymph node dissection, Osugi et al. compared 77 patients with squamous cell cancer who underwent minithoracotomy to 72 controls who underwent conventional three-stage treatment. Exceptional outcomes were obtained in terms of lymph node retrieval (33 vs. 32), operating time (227 vs. 186 min), reduced vital capacity (15% vs. 22%, p = 0.016), 3-year survival (70% vs. 60%), and 5-year survival (55% vs. 57%) [44]. Resection via thoracoscopy showed almost similar results to open esophagectomy. Moreover, surgical trauma was reduced. The differences in outcome between the first 34 and the next 46 patients who underwent surgery in the same study group demonstrated the impact of the learning curve on obtaining shorter operating times and better results by using this approach. Other advantage is that greater experience helps reduce postoperative pulmonary complications (5% incidence). Reduced blood loss, shorter operating time for thoracoscopy, reduced postoperative respiratory complications and higher lymph node retrieval were all observed in the last group [44]. In a study conducted on 222 patients undergoing thoracoscopic and laparoscopic esophageal resection, Luketich et al. (Ann Surg 2003; 238:486–494) showed an incidence rate of pneumonia of 7.7%. A significant finding was the reduced length of intensive care unit stay (1 day) and hospital stay (7 days) and the 1.4% operative mortality. Quality of life indicator was comparable to baseline scores and population standards. Nguyen et al. [47] assessed 46 consecutive patients and found similar results to Luketich et al. There have also been studies supporting robot-assisted thoracoscopy; however, there is still need for further investigation regarding robotic esophagectomy [48].

The results obtained by Biere et al. [49] in the TIME (Traditional Invasive vs. Minimally Invasive Esophagectomy) trial comparing the outcomes of 115 British patients who underwent either E or MIE showed that besides a decrease in perioperative pulmonary complications, the two procedures were more or less similar. However, the main competence of the trial was to show differences in short-term outcomes, with lower capacity in pointing out other outcomes. Patient outcomes were adapted to a population, improving the ability to perform a multivariate analysis of small differences in survival. There are few data on comparative differences in robot-assisted esophagectomy. In a study conducted on 43 patients who were treated with MIE (of which 11 underwent robot-assisted esophagectomy), Weksler et al. [50] reached the conclusion that robot-assisted and conventional procedures were similar. There were not enough patients included in the study, the results were disorganized, and there were no cancer data. Our study also experiences difficulties due to this aspect when comparing robotic with conventional MIE, but we managed to explain certain confounding variables for our outcomes. The limitations of our study are represented by the inability to determine specific MIE approaches (the McKeown procedure, the Ivor Lewis approach, and the transhiatal procedure). Earlier studies have demonstrated that the three procedures have similar outcomes, even though there are differences in terms of perioperative complications [51]. Another drawback was the difficulty in differentiating between patients who underwent hybrid procedures, such as laparoscopy combined with minithoracotomy, and patients who were treated with total MIE. These limitations pave the way for the occurrence of unknown interactions and confounding variables. Currently, there are two different clinical trials comparing E to MIE patients, namely the French MIRO trial [52] and the British ROMIRO trail [53]. Still, the study that we conducted is the most extensive comparative effectiveness research of MIE assessing long-term survival. As a result, MIE determines poor improvement in perioperative outcomes, with no negative impact on survival rates.

4. Combined modality therapy

4.1. Neoadjuvant chemotherapy

The use of preoperative chemotherapy compared with surgical treatment has been assessed in randomized trials in order to obtain improved surgical outcomes. However, the results are highly disputed. The three meta-analyses built on these randomized trials showed no difference in survival when the endpoint was 1-year survival in six of these trials. On the contrary, in comparison with surgical treatment, 2-year survival rates were improved following preoperative chemotherapy (4.4%) when the endpoint was 2-year survival in seven randomized trials [53]. When the meta-analysis was restricted to four recently randomized trials based on cisplatin and 5-fluorouracil therapy, there was a 6.3% improvement in 2-year survival. Still, this increase did not occur in one meta-analysis where the endpoint was 2-year survival [54]. The impact of preoperative chemotherapy is still uncertain.

4.2. Neoadjuvant chemoradiotherapy

Used in Europe and America since the end of the 1980s, preoperative chemoradiotherapy determined survival rate improvement in patients with cancer of the esophagus. Despite being used on a small scale due to the advanced surgical procedures available in Japan, a randomized trial reported the efficiency of hyperthermochemoradiotherapy in esophageal cancer [55]. Five meta-analyses built on five to seven randomized trials assess the impact of surgery alone, on the one hand, with preoperative chemoradiotherapy used in combination with surgery, on the other hand. There were no improvements in survival rates following preoperative chemoradiotherapy when the endpoint was 1-year or 2-year survival. When the endpoint was 3-year survival, there was an increase in perioperative mortality within 90 days after surgery, contrasted by a decrease in local recurrence and an improvement in 3-year survival rates in analogy to surgery alone (Int J Hyperthermia 1992; 8:289–295). There was a 14% decrease in death risk following preoperative chemoradiotherapy when the endpoint was the hazard ratio of survival curves [56]. Several reports [57–59] of six randomized trials showed higher survival rates following preoperative chemoradiotherapy than after surgery alone. Another report focusing on esophageal adenocarcinoma reported much higher survival rates following preoperative chemoradiotherapy versus surgery alone [60].

A meta-analysis of randomized trials conducted in Europe and America reported no improvement in survival with postoperative chemotherapy following curative resection in patients with cancer of the esophagus. In contrast, a randomized trial conducted in Japan showed that postoperative chemotherapy determined a major improvement in disease-free survival. In conclusion, postoperative chemotherapy recommends itself as an efficient measure to prevent recurrence after surgery.

4.3. Adjuvant radiotherapy

Four randomized trials assessing the differences between surgery alone and postoperative radiotherapy (45–65 Gy) reported no major improvements in survival. However, there was a decrease in local recurrence in the irradiated area following postoperative radiotherapy. No major improvements in survival were observed in a meta-analysis of these randomized trials. In conclusion, postoperative radiotherapy is not a conventional treatment option.

4.4. Postoperative outcome

The incidence of postoperative mortality was assessed in a considerable number of studies [61–65], fewer assessed in-hospital mortality, and 30-day mortality was determined in two studies [66]. Values were higher in patients who were treated with salvage esophagectomy after definitive chemoradiotherapy (23 patients—9.50%) than in patients who treated with planned esophagectomy after neoadjuvant chemoradiotherapy (29 patients—4.07%). Pooling of results validated the much higher incidence of postoperative mortality in the case of salvage esophagectomy (prevalence odds ratios (POR) = 3.02; 95% CI 1.64–5.58; $p < 0.001$).

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Chapter 3

Minimally Invasive Esophagectomy

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69584

Abstract

Minimally Invasive Surgery (MIS) for esophageal carcinoma has improved the outcome of patients. This approach has been shown to decrease the rate of respiratory complications, the intensive care unit (ICU) stay, and to allow a faster recovery of patients. Also, an improvement in perioperative care has contributed to better outcomes compared to the open approach. MIS has been shown to be as safe as open surgery in terms of resectability, harvested lymph nodes, and overall survival.

Keywords: esophageal carcinoma, anesthesia, minimally invasive esophagectomy, thoracoscopic esophagectomy, laparoscopic esophagectomy, surgical technique, prone position, postoperative care, postoperative prognosis

1. Introduction

Neoplasm of the esophagus is one of the most aggressive diseases with poor survival rate despite of the improvements in staging procedures, multimodality treatments, supportive care, and surgical techniques. It is the eighth most common cause of cancer and the sixth leading cause of cancer death worldwide [1]. Patients often are diagnosed at an advanced stage with metastatic disease in more than 50% at the time of presentation. Surgery is the gold standard for treatment both for early stage disease and for advanced disease after chemoradiotherapy neoadjuvant treatment. Surgery of esophageal cancer is probably one of the most demanding and challenging procedure for the surgeon and the patient alike—with a significant morbidity and mortality, particularly in inappropriately selected patients. Surgical treatment must consist on a radical R0 en-bloc esophagectomy associated with a two-field lymphadenectomy [2].

Traditionally, open approaches have been used to resect esophageal cancer, performed by transhiatal, transthoracic, or combined approach. Esophagectomy is a complex challenge for the surgeon, dealing with wide areas of the neck, mediastinum, and abdomen. Open esophagectomy is considered to be one of the most traumatic oncologic procedures performed in gastrointestinal surgery because of the extent of resection and dissection required [3]. It entails a significant risk of morbidity (at least a half of patients develop complications) and mortality, that ranges from 6–7% in high-volume centers to 20–28% in low-volume centers.

Orringer et al. [4] reported a large series of 1085 patients who underwent open esophagectomy by transhiatal approach, which has served as a standard to compare postoperative outcomes: hospital mortality rate of 4%; 53% of patients were discharged by 10th postoperative day; and an anastomotic leak rate of 13%. The most frequently reported complications of open approach have been pneumonia (21%), respiratory failure (16%), prolonged ventilatory support more than 48 h (22%), according to the report published by Bailey et al. [5].

In an attempt to avoid extensive tissue aggression and reduce the high morbidity and mortality, the minimal invasive approach has been introduced in the field of gastroesophageal surgery [6]. Cuschieri et al. [7] and DePaula et al. [8] were the first to apply a laparoscopic approach to patients with esophageal cancer. Cuschieri et al. performed six subtotal endoscopic esophagectomies through a right thoracoscopic approach with a mean duration of stay in the ICU of 19 h (range 16–26 h) and a median hospital stay of 11 days (8–18 days). DePaula et al. reported a small series of 12 patients who underwent transhiatal esophagectomy conducted by videolaparoscopy with no mortality and minimal blood loss.

Thanks to the improvements in technology and instrumentation, as well as the surgeons' training in advanced minimally invasive procedures, the practice of this technique has been extended since the 1990s. There are several single institution series reports [7–10] (retrospective and prospective) comparing Minimally Invasive Esophagectomy (MIE) versus open surgery [11, 12], and recent meta-analyses [13, 14] that have confirmed the safety and feasibility of the procedure and the advantages of minimally invasive surgery. These reports show that MIE can reduce the mortality and morbidity of open operations as well as allow a faster recovery. All these findings have been confirmed at the only available level I evidence study, the TIME-trial [15].

2. Patient selection

Tumor staging is essential for planning surgical treatment, and surgery should not be performed for patients without a chance of cure, such as those with distant metastases, or in those unable to survive the physiologic insult of the operation. The main objective of surgery must be to achieve a R0 resection. Nowadays, neoadjuvant chemoradiation plays a key role because it downstages the tumor and allows an adequate micro and macroscopic tumoral resection. From a surgical perspective, the drawback is that it may further complicate the procedure by distorting the peri-esophageal microanatomy and by causing a significant postradiation fibrosis. Tissue plane may be unclear and surgery will not be easy in this situation.

The difficult dissection as a result of neoadjuvant therapy and surgeons' fear to use a minimally invasive approach in advanced tumors, especially during their learning curve, cause an important discussion about MIE effectiveness in these situations. In a multicenter, open-label, randomized controlled trial published in 2012 by Biere et al. [15] that compares open surgery with MIE in advanced tumors, both with a similar number of patients, did not show significant differences between both in terms of margins resection. Thus, the minimally invasive approach would not be a contraindication in advanced stages. However, a previous history of abdominal or thoracic surgeries due to a significant underlying adhesion process could represent a real hindrance for minimally invasive technique.

3. Evaluation of physiological reserve

Predicting which patients are going to develop complications is not easy. Even so, we must know which indicators can increase postoperative morbidity and mortality. Many risk factors have been identified: Karnofsky score less than 80, liver cirrhosis, chronic obstructive pulmonary disease (COPD), ischemic heart disease, advanced age, locally advanced tumor, active smoking, alcoholism, and malnutrition [16–19] are some of them. Evaluating individual risk is important for patient selection and a proper preoperative management, regardless of the surgical approach to be performed (MIE or open surgery). However, there are physiological conditions of patients that cannot be improved.

The risk factors suggestive of preoperative optimization are the following:

- In cases of COPD, the use of long-acting β-agonists, combined with inhaled steroids [20, 21] and preoperative inspiratory muscle training, may reduce postoperative pulmonary complications [22].
- If significant coronary ischemia is discovered in perioperative time, coronary revascularization with angioplasty and stenting could be performed, although antiplatelet agents prescribed after this technique could delay esophagectomy.
- Alcoholism and smoking—The UK National Institute for Health and Clinical Excellence (NICE) recommends the use of nicotine as a replacement therapy for smokers to help stop smoking, because smoking is associated with higher risk of 30-day mortality and serious postoperative complications [23].
- Malnutrition is considered an independent risk factor that influences the development of postoperative infections, mortality, length of stay, and hospital costs in patients undergoing surgery [24]. We must bear in mind that most patients with esophageal neoplasia have difficulties for an adequate intake, which generates poor nutritional status and immunosuppression. Therefore, patients with nutritional risk screening (NRS) score ≥3 should have an optimized nutritional support that includes both enteral nutrition to maintain the intestinal barrier function and parenteral nutrition to avoid malnutrition and infection due to long-term insufficient feeding. These measures will help to improve clinical outcomes in these patients [25, 26].

- Patients who have a Forced Expiratory Volume in one second (FEV 1) < 70% of the predicted normal in the pulmonary function tests with normal arterial gas blood measurements are considered of moderate risk and those with FEV 1 < 50% or if the arterial gas bold analysis show hypoxemia or carbon dioxide retention must be considered of high risk.
- Patients with Child C stage cirrhosis must not be eligible for surgery.

4. Anesthetic challenges of MIE

The anesthetic challenges of MIE include prolonged surgery, difficulties of lung isolation, and one lung ventilation (OLV) when patient is positioned right up and complications related to extraperitoneal CO_2. Pain relief has been described as a protective factor to avoid postoperative respiratory complications, so it is highly recommended to use regional techniques for reducing postoperative pain. Also, the amount of fluids administered perioperatively can lead to the development of pulmonary complications and should be adequately evaluated to avoid fluid overload.

4.1. Prolonged surgery

MIE is a long procedure and may extend at least 5–6 h, depending on the experience of the surgeon. Such prolonged surgery increases the risk of hypothermia which can lead to reduce oxygen delivery and increase myocardial work, stress response, and postoperative infection. Our main objective is to maintain normothermia. If at the end of the surgery the patient is normothermic, extubation will be possible and postoperative ventilation will not be necessary [27].

Balanced anesthesia, by an inhalation approach (sevoflurane and desflurane) or by propofol target-controlled infusion with remifentanil, may help promote early recovery after MIE. There is evidence that both sevoflurane and desflurane, when compared with propofol, produce a beneficial local immunomodulatory effect in patients undergoing OLV for thoracic surgery, significantly reducing inflammatory mediators, adverse postoperative events, and improving clinical outcomes [28, 29].

4.2. One lung ventilation

MIE with a patient in right up position requires a period of one lung ventilation during the mobilization of thoracic esophagus. Inadequately managed lung isolation contributes to mortality and morbidity [30].

When surgery is performed thoracoscopically, retraction of an inadequately collapsed lung or lobe results more difficult than in open surgery, and this is important when choosing the method used to achieve lung isolation. The options described to reach an adequate lung isolation are a left or right double lumen tube or a single lumen tracheal tube and a bronchial blocker. A retrospective study has not found differences in intraoperative hypoxemia, hypercapnia, and high airway pressures whether a left- or right-sided tube was placed for OLV [31].

As a consequence most MIE techniques involve access to the right thorax; a left double-lumen tube perhaps would be preferable, especially when the thoracic approach is done in lateral decubitus. If we used the prone position (PP), a single-lumen endotraqueal tube is a valid alternative. Whichever method of lung isolation is selected, a fiberoptic bronchoscope should be used to check correct positioning both after intubation and after moving the patient before surgery [32].

The combination of OLV and esophageal surgery results in an inflammatory response that will increase alveolar injury, leading to the development of acute lung injury (ALI) [33]. During and after OLV, the alveolar concentrations of IL-6 and IL-8 are increased. The lung protective ventilatory strategy can reduce airway pressure and airway resistance. It can decrease the release of IL-6 and IL-8 and inhibit lung inflammatory response during OLV and postoperatively [34]. Some of the consequences that may cause ventilator-induced lung injury are volutrauma (high tidal volume), barotrauma (excessive transpulmonary pressure), atelectrauma (repeated opening and closing of alveoli resulting), and biotrauma (caused by inflammatory mediators) [35].

Thus, it is essential for the implementation of protective ventilatory strategies to reduce the severity of lung injuries during mechanical ventilation. These strategies include restrict tidal volume to 5–6 ml/kg during OLV, optimizing positive expiratory end pressure (PEEP), and limiting plateau and peak inspiratory pressures to less than 25 cm H_2O and less than 35 cm H_2O, respectively [36]. In addition to reduce lung injury, these actions promote early extubation [37].

4.3. Complications of extra-peritoneal carbon dioxide

MIE may require a large period of capnoperitoneum, while laparoscopic dissection and mobilization of the stomach are being performed. As a consequence of surgical communication between the chest and abdomen, carbon dioxide may pass into the right chest, where drain tube has been placed in thoracic step, and this gas can be vented by this drain. In this situation, laparoscopic abdominal dissection could be difficult. Moreover, carbon dioxide may diffuse into the mediastinum (capnomediastinum), into the left chest, and it can cause subcutaneous emphysema around the chest, axilla, and neck. We can realize that gas is spreading to these spaces if we object a rapid increase in end-tidal CO_2. If CO_2 is accumulated inside thorax cavity, an increase of airway pressures and lung compression might occur, leading to oxygen desaturation. This fact could negatively affect cardiac output.

We can solve all these problems by reducing the pressure at which the capnoperitoneum is maintained, and this will reduce the diffusion of gas to thoracic cavity without impairing abdominal dissection. Anyway, if extra-abdominal CO_2 compromises cardiac or respiratory function, the capnoperitoneum should be evacuated. We should not extubate patients with significant emphysema until we achieve normocarbia [27].

4.4. Fluid management—goal directed therapy (GDT)

Maintaining adequate fluid balance is essential in both open surgery and MIE. While excessive fluid administration may be associated with increased postoperative pulmonary complication, tissue edema, and compromised perfusion, an inadequate intravascular volume can predispose to ischemia, end-organ dysfunction, and risk of anastomotic failure and leak.

In esophagectomy patients, an accurate fluid balance is essential to achieve adequate perfusion pressure and oxygen delivery to vital organs. The form of fluid replacement therapy, which is currently recommended, seems to be based on the principles of goal-directed therapy (GDT) with the aim to increase cardiac output in high-risk surgical patients. Various studies have found that GDT-based fluid administration improves intraoperative hemodynamic stability and reduces intensive care unit admissions, the incidence of complications, and mortality [38].

Some authors have suggested that restrictive fluid therapy is preferable to fluid overload because it leads to improved gastrointestinal recovery time, reduced overall morbidity [39], improved respiratory parameters, decreased incidence of postoperative pulmonary complications and shorter recovery periods [40]. On the other hand, fluid overload causes lung injury and has negatively impact to intestinal anastomoses [41].

4.5. Thoracic epidural analgesia (TEA) versus paravertebral analgesia

Even with reduction in trauma access, MIE may still result in an important postoperative pain, and optimal multimodal analgesia is required. Effective analgesia accelerates extubation, recovery, and early mobilization. Despite the importance of regular postoperative simple analgesia, a regional technique is essential.

Thoracic epidural analgesia (TEA) offers many benefits in esophagectomy, reducing respiratory complications, such us pneumonia [42–44] and postoperative pain. TEA has also been associated with decreased incidence of anastomotic leakage [37], possibly as a consequence of improving microcirculation in the gastric conduit [45]. Moreover, epidural analgesia also decreases the risk of prolonged ventilation or reintubation and improves some lung function parameters and blood oxygenation [46]. However, TEA also has some disadvantages: the incidence of failure may reach 12%, there are risks in the application technique, and it does not only promote urinary retention but also cause hypotension which makes necessary additional fluid administration [47–49]. Contraindications to an epidural access include sepsis or bacteraemia, infection at the insertion site, hypovolemia or shock, coagulopathy or thrombocytopenia and increased intracranial pressure [50].

Paravertebral blockade has recently been shown to provide analgesia comparable with TEA after thoracic step of esophagectomy. It is associated with less incidence of failed block and reduces hypotension and urinary retention when it is compared with TEA. Several recent reviews and meta-analyses defend its benefits [51–53], and it is a standard practice in some UK hospitals for minimally invasive esophagectomy. Local data also show shorter stays in the intensive therapy unit comparing with TEA.

4.6. Conclusion

MIE supposes many anesthetic challenges, some of them unique for this type of procedure and requires an accurate knowledge of the different surgical steps performed. Moreover, it is essential to know and treat complications of one lung anesthesia and extra-peritoneal spread of CO_2. Paravertebral blockade might have more benefits than TEA to improve postoperative pain in patients undergoing for MIE.

5. Operative technique

Minimally invasive esophageal resection for cancer involves a three-stage operation that includes a thoracosopy and laparoscopy, either with a cervical or intrathoracic anastomosis. It has been described as different combinations of laparotomy, thoracotomy, thoracoscopy, and laparoscopy approaches called hybrid techniques. These techniques have 1 step of the procedure completed via an open approach.

5.1. Thoracoscopy phase

The operation starts with thoracoscopic mobilization of the esophagus and thoracic lymphadenectomy. The thoracic phase can be performed through a lateral right thoracic approach by blocking the right tracheal bronchus, or in prone position without selecting any blocking.

In the first case, the patient is positioned in the left lateral decubitus position (LDP) and a right lung blocking is achieved employing a double-lumen tube. The surgeon stands on the left side of the patient and the assistant on the right. Three to four thoracoscopic ports are used in this approach and placed as follows:

- 10-mm camera port is placed at the 7th to 8th intercostal space, just anterior to the midaxillary line.
- A 5-mm port is placed at the 8th or 9th intercostal space, posterior to the posterior axillary line.
- A 10-mm port is placed at the 4th intercostal space in the anterior axillary line.
- The last 5-mm port is placed just posterior to the scapula tip.

When thoracoscopy is performed in a prone position (**Figure 1**), the mobilization of the esophagus takes place with a right prone posterior approach. Patients are intubated with a single-lumen endotracheal tube and the right lung remains partially collapsed because of the positive pressure of pneumothorax created and due to the gravity. The right upper limb is abducted 80–100°. The surgeon stands on the right side of the patient, the first assistant (camera) to the left of the surgeon, and the second assistant stands on the left side of the patient. Three ports are used and placed as follow:

- 10-mm camera port is placed at the 7th intercostal space below the inferior angle of the scapula.
- 5–10 mm port for right-hand working is placed at the 5th intercostal space right lateral from the spinous process.
- 5 mm for left-hand working is placed at the 9th intercostal space right lateral from the spinous process.

Figure 1. Thoracic trocar position on the right chest for thoracoscopic esophagectomy.

Pneumothorax is created and the insufflation pressure must be maintained at 6–8 mmHg. A single retracting suture in the diaphragm could be used to provide downward traction allowing good exposure of the distal esophagus, although in most occasions this is not necessary.

After a general survey of the tumor area and pleura, the inferior pulmonary ligament and the mediastinal pleura over the esophagus are divided up to the level of the azygos vein (**Figure 2**), which is sectioned with an endoscopic vascular stapler. The proximal esophagus is exposed and dissected circumferentially up to the level of 1–2 cm above the carina, using 5-mm harmonic shears, from the pericardium, chest wall, descending thoracic aorta, and superior cava vein, including all surrounding lymph nodes (**Figure 3**), periesophageal tissue, and fat. A tape is used for retraction of the esophagus to facilitate the dissection around it. Any aortoesophageal vessel and any lymphatic branches must be clipped. The thoracic duct has to be protected. The vagal trunks are identified and divided.

The dissection should be performed near the esophagus to avoid trauma to the posterior membranous trachea and the recurrent laryngeal nerves, which is the most difficult step. Laterally, dissection is carried down to the left pleura and continues to the thoracic inlet. A careful lymph nodal clearance must be achieved in the supracarinal space. Mobilization of the distal esophagus poses no problem, and it is important to limit it in order to avoid difficulty in maintaining pneumoperitoneum during the abdominal phase.

After the placement of a chest tube, the right lung is allowed to expand fully (or inflated in left lateral decubitus approach). Some surgeons infiltrate intercostal spaces with local anesthetic. Trocars are removed, and ports are closed.

http://dx.doi.org/10.5772/intechopen.69584

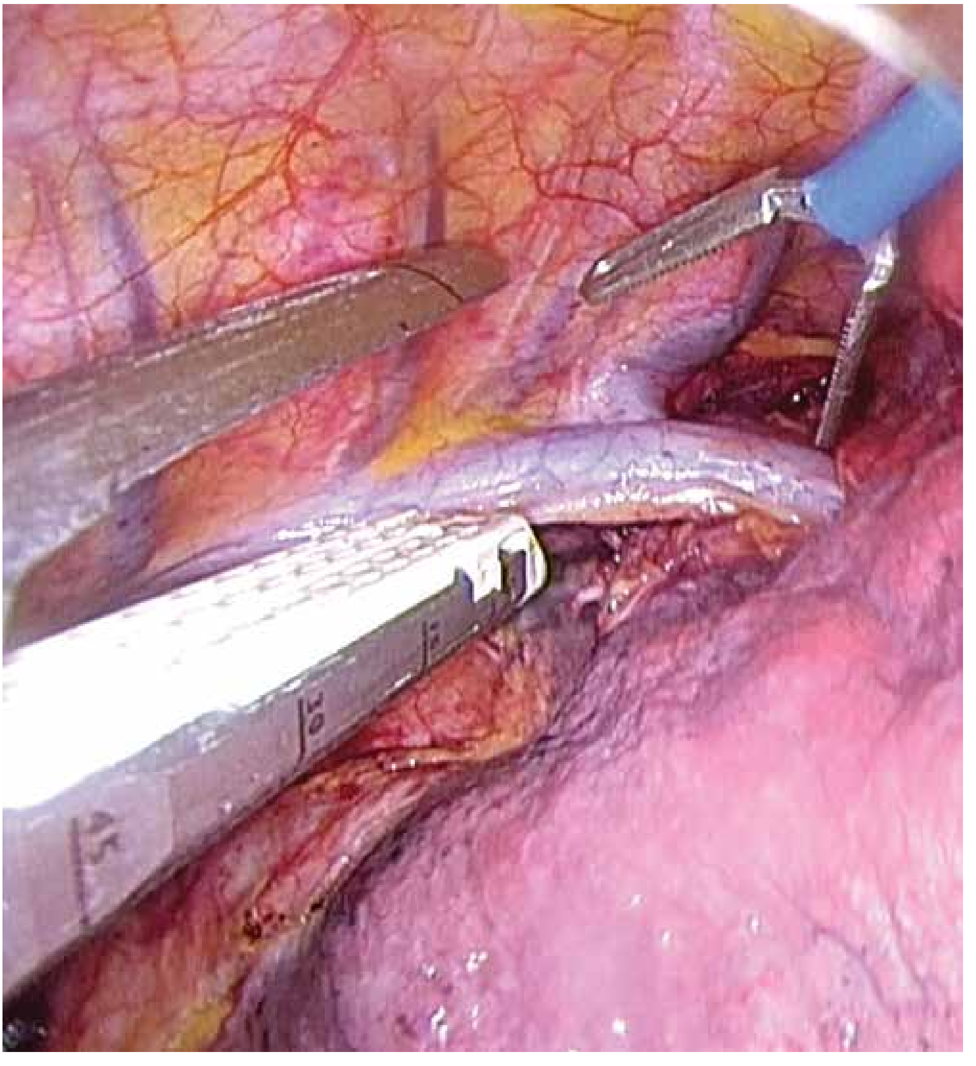

Figure 2. Division of the azygos vein using a stappler.

5.2. Laparoscopy and cervical phase

The second stage starts turning the patient to a modified Lloyd-Davis position with reverse Trendelemburg and neck exposing the left cervical area. The surgeon remains between the legs of the patient. The first and second assistants stand to the right and to the left of the patient, respectively. Five abdominal ports are used for the dissection: 10-mm supraumbilical port for camera; 5 mm epigastric port for retraction of left lobe of the liver, 5–10 mm right midclavicular port for left-hand working; 5–10 mm left midclavicular port for right-hand working; and 5–10 mm left anterior axillary port for gastric retraction. It is advisable to use trocars of a diameter of 10 mm for the possibility of using staplers from any port.

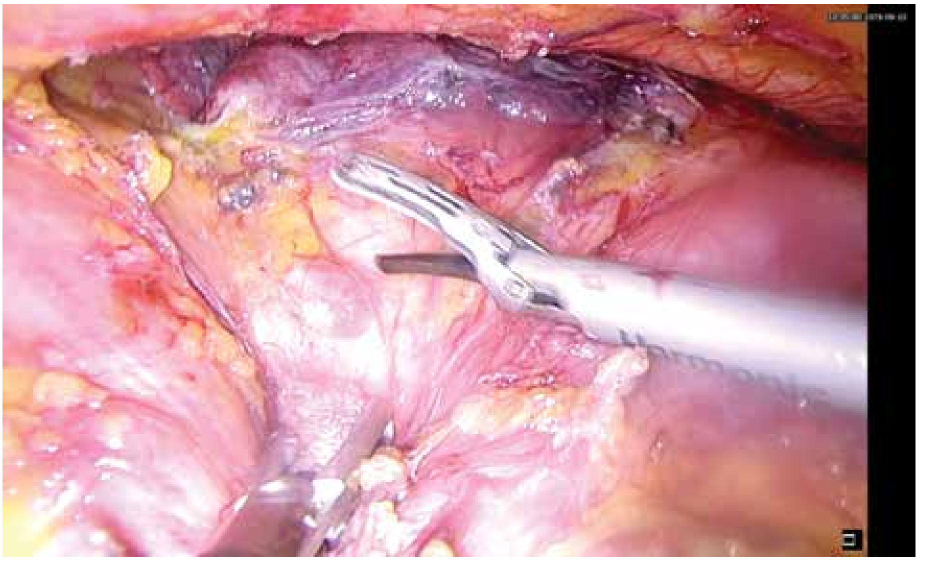

Figure 3. Mediastinal periesophageal lymph node.

After placement of the ports, an abdominal general survey must be performed. The gastrohepatic omentum is divided; the right and left crura of the diaphragm are dissected to allow easy passage of the gastric tube through the hiatus (preventing later gastric outlet obstruction). Left gastric artery and vein are dissected and divided using an endoscopic stapler with vascular load and a careful lymph node clearance over the left gastric pedicle, celiac axis, common hepatic, and splenic artery must be achieved. The stomach is mobilized by dividing the short gastric vessels in the gastrocolic omentum, using ultrasonic coagulating shears taking care of preserving the right gastroepiploic arcade. The fundus is dissected from the superior pole of the spleen and the pancreaticogastric ligaments are divided. Authors do not recommend pyloroplasty since it has been widely demonstrated that this does not improve gastric emptying.

Then the gastric tube is constructed with the stapler by dividing the stomach starting at the lesser curve. The construction of the gastric tube may vary depending on the characteristics of the tumor (if the tumor is located in the gastroesophageal junction or it has gastric extension, it may be necessary to resect some of the proximal stomach and to make an intrathoracic anastomosis). It is preferably a gastric tube with 5–6 cm in diameter. Most of the groups place a feeding jejunostomy laparoscopically. Authors prefer to leave a nasojejunal feeding tube to avoid complications derived from a jejunostomy.

The phrenoesophageal membrane is dissected, and gastric conduit is pulled through posterior mediastinum and brought up to the neck. Torsion is avoided by ensuring that the greater curvature always lies toward the left crus.

The last stage consists of a careful dissection of the cervical esophagus. A 4–6 cm left skin crease cervical incision is made. The tape looped around the esophagus left during the thoracic dissection allows the surgeon to pull it out through the neck to facilitate the dissection. The esophagogastric specimen is pulled out of the neck incision and the esophagus is transected 2–3 cm distal to the upper esophageal sphincter. A very high anastomosis is performed between the cervical esophagus and gastric tube in an end-to-end manner using an End-to-end anastomosis stapler (EEA sta-pler) or something similar. Some groups suture the gastric conduit to the prevertebral fascia. Neck wound is closed and a cervical drain could be placed. To prevent hiatal herniation, laparoscopic tacking sutures between the gastric tube and the diaphragm should be placed. If the anastomosis is performed intrathoracicaly, cervical stage is not performed.

Some groups pull out the specimen through a minilaparotomy incision incorporating camera port, and they construct the gastric tube in an extracorporeal way. This is recommended in cases of bulky tumors because it facilitates extraction of the specimen and allows to achieve a longer gastroplasty in case of performing the anastomosis in the neck.

One tube-drain is placed close to the hiatus. Trocars are removed, and ports are closed.

6. Minimally invasive surgery versus open approaches

Minimally invasive esophagectomy emerges as an attempt to reduce the significant morbidity and mortality of classic open techniques and allows a faster recovery of the patient.

Different groups have reported their experience in implementation of minimally invasive surgery in esophageal cancer in order to assess the potential advantages and disadvantages. One of the largest series was published by Luketich et al. [9]. They showed their outcomes in 222 patients after MIE: 30-day operative mortality of 1.4%, median intensive care unit stay of 1 day (range 1–3), hospital stay of 7 days (range 3–75), lower incidence of pneumonia, and adult respiratory distress syndrome (ARDS) (7.6 and 5%, respectively); anastomotic leak rate of 11.7%; and excellent health-related quality of life (HRQL) scores at a mean follow-up of 19 months, showing that MIE is a safety procedure and have potential advantages over open approach. Palanivelu et al. [10] reported their experience in 130 patients who underwent MIE with prone thoracoscopy: median ICU stay of 1 day (range 1–32 days), median hospital stay of 8 days (range 4–68 days), postoperative morbidity of 20.76%, perioperative mortality of 1.54%, anastomotic leak rate of 2.31%, lower incidence of pneumonia, and ARDS (1.54 and 0.77%, respectively), minimum blood loss. Both series showed a stage-specific survival similar to an open approach.

These findings have been confirmed in a recent meta-analysis [13] of 57 studies containing 15,790 patients with resectable esophageal cancer. Less intraoperative blood loss, short hospital stay, reduction of the incidence of total and pulmonary complications (OR: 0.700, 95% CI 0.626–0.781 and OR: 0.527, 95% CI: 0.431–0.645, $p < 0.05$, respectively), and high operative time than Open esophagectomy were found. However, ICU stay, the number of harvested lymph nodes, and anastomotic leak had no significant differences.

As we have mentioned previously in this chapter, traditional open esophagectomy carries a significant risk of postoperative complications that involves a profound detrimental impact on patient's quality of life. Quality of life typically returns to baseline after 1 year [54]. Minimally invasive techniques avoid thoracoabdominal incisions and reduce the levels of tissue trauma. The recovery rate after minimally invasive esophagectomy seems to be faster than after open approach. Parameswaran et al. [11] assessed this question in a prospective longitudinal non-randomized study in 62 patients, measuring health-related quality of life (HRQL) after MIE. Their study noticed that although patients reported marked deterioration in most aspects of HRQL 6 weeks after the operation, they started to recover by 3 months and returned to baseline levels by 6 months, except reflux and diarrhea.

There is concern about if oncologic outcomes are equivalent to that of the open approach. When minimally invasive surgery was introduced in the management of colorectal cancer, there was also a concern about safety and oncological quality of resections. However, several randomized prospective trials demonstrated that the laparoscopic approach was not only safe but also oncologically sound [12].

While the advantages over short-term postoperative outcomes have been widely published by different institutions, there is a lack on the available data about oncologic efficacy and survival after MIE compared with the open approach. Different groups have tried to demonstrate that the adequacy of surgical margins and lymphadenectomy can be maintained or even improved with a MIE approach [55]. Berger and colleagues [12] found in their retrospective review that there were no differences between the groups in the R0 resection rates and a significant increase in nodal harvest in the MIE group (median 20 versus 9; $p < 0.0001$). Because of the known impact of neoadjuvant treatments on lymph node yields, they also examined lymph node harvest by the presence or absence of neoadjuvant chemoradiation, and they did not find differences in both groups. However, patients in the open group had a more advanced stage disease, and most of them had received neoadjuvant treatments.

The same group published a later work, Palazzo et al. [56], that compares survival of patients undergoing MIE and open or hybrid esophagectomy (OHE) in a retrospective analysis. They found on Kaplan-Meyer univariate analysis, a significantly improved 5-year survival with MIE (MIE 64%, OHE 35%, $p < 0.001$) and after adjusting for potential confounding factors (lymph nodes harvested, neoadjuvant treatments, stage, etc.) in a multivariate analysis demonstrated that patients undergoing OHE had a significantly worse survival. They made the same selection bias as in their previous study.

Nevertheless, these results are based on nonrandomized small series with heterogeneous data and could be affected by patient selection bias (frequently MIE group include a higher number of patients who have early disease stages and thus, less patients who received neoadjuvant chemoradioteraphy). Advanced tumors and the use of neoadjuvant therapy have been considered to be contraindications to MIE by many surgeons and limited its use, especially in patients with advanced disease.

All these studies have culminated in TIME-trial published in *The Lancet* in 2012 by Biere et al. [15, 57]. It is the first randomized trial to investigate the potential advantages of minimally invasive esophagectomy. They undertook a multicenter, open-label, randomized controlled trial at five study centers in three different countries. They compared open with minimally invasive esophagectomy with a right thoracoscopy in the prone position in a total of 115 patients with resectable esophageal cancer, excluding cervical allocation. The results showed that significantly fewer patients had postoperative pulmonary infections, shorter hospital stay, and less blood loss in the minimally invasive group than in the open group. No difference was found in ICU stay. Also, short-term postoperative quality of life measured by SF 36, EORTC C30, and esophageal-specific OES18 questionnaire were significantly better for patients in the minimally invasive group, and they had less pain according to the Visual Analogue Scale (VAS) pain score. However, pathological parameters of the resected specimen and 30-day and in-hospital mortality did not differ between groups. They concluded that patients undergoing the minimally invasive approach have short-term benefits in pulmonary infections, hospital stay, and quality of life outcomes with no compromise in the quality of the resected specimen.

More randomized clinical trials are needed in order to assess the long-term advantages of minimally invasive surgery.

7. Prone position versus lateral decubitus position for thoracic step

To minimize morbidity and mortality after an esophagectomy, a thoracoscopic approach was introduced as a minimally invasive option [58, 59]. This procedure is most commonly performed with the patient in the left lateral decubitus position, but prone position is a valid alternative. Cuschieri et al. [60] first explained the prone position (PP) for thoracoscopic esophageal mobilization in 1994. They described this technique in 6 patients and compared the results with those of left lateral position in 20 patients. They suggested that PP had technical advantages and reduced postoperative complications. However, this technique was not widely used at that time, and more than 10 years have passed by to find publications that talk about PP again. In 2006, Palanivelu et al. [10] reported their experience with 130 patients treated by thoracoscopic esophagectomy in PP raising new interest in this procedure. Many reports about that have been published so far.

The primary benefit of the PP is derived from the anatomical exposure: the lung falls away as a consequence of gravity and the esophagus is better visualized. This permits performance of the operation without the need for collapsing the right lung using a double-lumen endotracheal tube. If we use a single-lumen endotracheal tube, the partial or intermittent ventilation of the right lung reduces the venous shunt effect and results in opening up a great percentage of the alveoli helping in prevention atelectasis. Moreover, this type of ventilation does not make difficult the surgical procedure or prolong its duration. In a prone position, we have better functional residual capacity than in a supine position. Furthermore, ventilation perfusion ratio is well maintained, and hypoxia and hypercarbia are avoided. All of this, aided by gravity, reduces lung injury. All that was mentioned previously could explain why Cuschieri et al. [60] described a decrease in respiratory complications in PP. Luketich group [9] performed the thoracoscopic surgery in LDP and reported the incidence of pneumonia in 7.6% and adult respiratory distress syndrome (ARDS) in 5% of the patients. Palanivelu et al. [10] talks about pneumonia in 1.54% of the patients and ARDS in 0.77% with PP approach.

As we have described already, gravity and artificial pneumothorax may improve mediastinal organs and structures exposure without any help of an assistant: this is another benefit of the PP. It makes possible the use of only three trocars, while four of them are needed in lateral decubitus approach. Prone position also promotes blood and other fluids from accumulating in the right anterior thorax, instead of posterior mediastinum that takes part of operative field. Thus, intermittent suction of accumulated fluids is not required during surgery. In the lateral position, the esophagus is in a dependent place and any pooling of blood obscures the surgical field.

Recently, Javed et al. [61] have published a comparative study between MIE in prone versus lateral decubitus position (LDP). They described the surgery in LDP using an additional trocar (four in total) for the assistant to retract the lung and to suction out the blood, whereas they only need three for PP technique. In this study, authors report low blood loss intraoperative, which was significantly less in PP group. Kubo et al. [62] also describe significantly lower blood loss with this approach. This fact could be explained due to a better exposure in PP that allows a more meticulous dissection avoiding damage to vessels and other thoracic structures and decreasing bleeding.

Noshiro et al. [63] have published a study to describe whether lymphadenectomy along the left recurrent laryngeal nerve is facilitated in the PP. Lymph nodes along this nerve are frequently involved by carcinoma cells, and their complete dissection is required [58]. They conclude that when PP is compared with LDP, lower blood loss and better exposure of the surgical field around the left recurrent laryngeal nerve occurs in first group. Although they describe slightly higher number of the resected lymph nodes in the PP, they do not find significant differences. On the other hand, Javed et al. [61] show a significantly higher lymph node yield in PP and the number of patients with affected lymph nodes is also significantly higher.

Most of the reports [10, 61] describe a shorter operative time for a thoracoscopic esophagectomy in PP than in LDP. As we have said before, the best exposure of the surgical field allows for faster and better quality surgery.

Fabian et al. [64] suggested that the learning curve for the prone position approach appears to be relatively short, within the first five cases. This author also says that prone approach may result in better dissection into the neck explained by pneumatic dissection from the thoracic cavity cranially along the esophagus. This maneuver simplifies the neck surgery that could lead to less morbidity in cervical step.

The incidence of complications, such as anastomosis leak, gastric tip necrosis, chylothorax, tracheal, or vocal cord injury is comparable between PP and LDP according to many reports. Other clinical outcomes seem to be similar between both: median length of stay, discharged within 10 days, and in-hospital mortality [63, 64]. As we have commented at the beginning, it might be possible to reduce respiratory morbidity using PP approach.

In addition, in PP the surgeon's wrist and shoulder joins are in a neutral position in relation to the forearms and upper arms, minimizing fatigue and maximizing ergonomic function. The view of the monitor stands parallel to operative field and ergonomic position of the surgeon makes easier hand-eye coordination. In contrast in LDP, the surgeon's view of the monitor must be turned upside down to avoid the counterimage when two monitors are set on each side. In this situation, hand-eye coordination cannot be obtained smoothly if a scope-holding assistant does not work correctly.

One disadvantage with the prone technique could be the need for conversion to open required electively when many adhesions preclude a minimally invasive approach or emergently as a consequence of uncontrollable bleeding. Although a posterior thoracotomy can be performed in this position, it is a less familiar approach that hinders dissection. Moreover, if we have performed the thoracic step without the use of a double-lumen endotracheal tube, we have to know that if a conversion is required, isolated lung ventilation would be invaluable. Thus, there are authors that continue using double-lumen intubation in the prone approach [64].

In conclusion, the PP may be performed with comparable outcomes to the LDP. The technique improves exposure of the operative field and reduces surgical times without compromising patient's safety or oncological results. Moreover, PP brings on an ergonomic position for the surgeon that makes easy the dissection.

8. Fast-track surgery (FTS) protocol on patient undergoing MIE

The concept of fast-track surgery (FTS) was first introduced by Kehlet and Mogensen [65], and the objective of his study was to show less postoperative stress, reduce morbidity associated with complications, accelerate recovery, and reduce postoperative cost in patients submitted for colon surgery after a rehabilitation programme [66]. It is essentially a multidisciplinary team to perform a fast-track approach during perioperative period for reaching an optimal outcome [67]. To date, the fast-track protocol has been applied in many surgical fields such as colon, rectum, or liver, but there is limited literature talking about the safety of using this protocol in esophageal surgery, especially in those cases where a minimally invasive technique is going to be performed.

Patients must receive health instructions and adequate information about FTS in the preoperative period. As we have explained previously, it is essential to optimize nutritional support with enteral and parenteral nutrition in those patients with long-term insufficient feeding and nutritional deficiencies. Recall that this measure has not been carried out in conventional care [68].

Many anesthesiologists have always been wary of allowing an esophageal cancer patient to ingest liquids 3 h before induction of anesthesia, defending the risk of aspiration pneumonia with this maneuver. But National and European Anesthesia Societies now recommend intake of clear fluids until 2 h before the induction of anesthesia as well as a 6 h fast for solid food [69]. Following these guidelines, Pan and his group, who have recently published a FTS protocol for MIE [70], instructed patients to drink fluid meals until 6 h before surgery and a carbohydrate drink until 3 h before surgery. They do not notice more pulmonary complications in FTS group than in conventional management group.

The use of the nasogastric tube (NGT) during the postoperative period is still controversial, although data describes disturbance of water, electrolyte, and acid base, and more digestive fluid reflux using nasogastric tube, which can increase pulmonary morbidity [71]. Some studies also show that NGT can delay normal gastrointestinal function [72]. Removal of NGT in the immediate postoperative period promotes early oral diet introduction that has some physiological advantages: decreases bacterial translocation, ensures function of intestinal mucosal cells, activates digestive secretory system, reduces postoperative infection, and accelerates organ recovery [73]. Oral feeding can be initiated during the first 48 h, following a stepwise programme from water to fluid meals, and finally to semifluid meals and normal food. Pan et al. [70] do not report gastroenterological complications, including anastomosis leak, without using NGT in postoperative period, and they suggest that an early oral diet in patients with MIE is safe and feasible. Enteral nutrition through jejunostomy may be initiated on the first postoperative day, even before oral intake. Both, oral and enteral nutrition, promote faster recovery of gastrointestinal function. Lewis et al. [74] concluded in their meta-analysis that early enteral nutrition can reduce anastomosis leakage and mortality. Jejunostomy can be removed when patients are able to ingest normal food.

The evidence about restrictive fluid administration intraoperatively and postoperatively, as we have reported in section called "anesthetic challenges of MIE," show less cardiopulmonary complications with this therapy. Earlier oral and enteral nutrition promotes that postoperative intravenous fluids can be reduced to as little as possible and removed during the first 24–48 h.

Abdominal and chest tube are also points of discussion in the FTS programme:

- Abdominal cavity drainage allows monitoring active bleeding and anastomosis leak, but it also can lead to abdominal infection and intestinal obstruction. While conventional care prefers to maintain drainage a few days, supporters of the fast-track protocol suggest that we should not leave drainage if there is no evidence of intraoperative complications. Jesus et al. [75] do not report more mortality or morbidity without using abdominal drainage.

- Chest tube causes pain and limits patient's mobility, so it has to be removed as soon as possible. A recent study has showed that it is safe to remove thoracic drainage when its volume is between 250 and 450, and there is no air leak.

The fast-track protocol also includes early perambulation after surgery for preventing venous thromboembolism that can be facilitated if patients are not carrying any type of drainage. Adequate analgesia can also accelerate perambulation and promote the recovery of intestinal function. Moreover, chest physiotherapy and incentive spirometry should be instituted. In their study, Pan et al. [70] reported that hospital stay and the days until intestinal activity are significantly shortened in the FTS group without an increase in morbidity and mortality. Patients undergoing MIE and fast-track protocol can be discharged earlier, even in the first week.

In summary, FTS program can be used safely in patients undergoing MIE because it promotes early recovery without increasing morbidity and mortality. We must offer the patient adequate preoperative information about the fast-track protocol to facilitate its implementation in the immediate postoperative period.

9. Conclusion

The minimally invasive approach to esophageal cancer is a safe and feasible procedure with favorable outcomes when compared to open esophagectomy. The data available reported by the different studies describe fewer respiratory complications, a reduction of hospital stay and faster patient recovery without compromising the oncologic efficacy related with harvested lymph nodes and R0 margin resection. The thoracoscopic approach in prone position is an alternative that offers more benefits than the lateral decubitus technique. Moreover, the implementation of a fast-track protocol allows an early recovery without increasing morbidity and mortality.

Acknowledgements

Thanks to Mrs. Noelia Tomás Marín-Baldo for her contribution in correcting English.

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Chapter 4

Radiation Therapy for Esophageal Cancer

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.70096

Abstract

Esophageal cancer develops in the mucosa of the esophagus and spreads toward the muscle layer. The nonsurgical treatment for localized, deeply invasive esophageal cancer has been external beam radiation therapy (EBRT) and concurrent chemotherapy. Recently, intraluminal brachytherapy showed a strong potential for the improvement of the therapeutic ratio. It was found that the fractionated high dose rate (HDR) brachytherapy offered beneficial palliation for a longer period of time with more durable symptom control. A similar was concluded for advanced unresectable esophageal cancer in previously irradiated patients. HDR brachytherapy may be a useful salvage treatment option for inoperable patients diagnosed with local esophageal cancer. Although better local control can be achieved with higher brachytherapy dose, this increases the risk of acute morbidity and late morbidity, especially in the setting of recurrence cancer. It was found that the moderate dose of EBRT and HDR brachytherapy could give a better local response than EBRT alone.

Keywords: esophageal cancer, radiation therapy, brachytherapy

1. Introduction

Esophageal cancer is the eighth most common cancer worldwide, besides being the sixth most common cause of cancer death. There were 456,000 new cases in the world in 2012 [1]. It is four times more common in men than in women; it occurs more frequently among people above 45 years of age and reaches its plateau among people at 65–74 years of age. Its mortality is high; it can be as high as 84%. For the locally advanced disease, the 5-year survival is 15–34%. The cornerstone of treatment remains surgery; however, there is evidence that survival is favorably influenced when additional therapies, such as chemotherapy or radiation therapy or their combination, or targeted therapies are used for lymph node-positive or cT2 or tumors that are larger than cT2. The clinical studies assessing treatment modalities for esophageal cancer are diverse: the modalities (chemotherapy, radiation therapy and surgery) have been evaluated in various orders and combinations. The number of study subjects has rarely been over 100 per study. The study populations have not always been homogeneous; different portions of the esophagus were affected, and the study population is sometimes mixed, regarding staging and histology.

1.1. Histology

Histology is usually based on the histologic analysis of an endoscopic sample. There are two main types of esophageal cancer: squamous cell carcinoma (SCC) and adenocarcinoma. Squamous cell carcinoma mostly occurs in the lining in the upper portion of the esophagus. Adenocarcinoma develops at the junction between the esophagus and the stomach. Most of the tumors are squamous cell carcinoma, but the incidence of adenocarcinoma has been increasing.

1.2. Predisposing factors

Intraepithelial neoplasias, such as epithelial dysplasias and in situ carcinoma, are the most significant precursor lesions for the development of esophageal cancer. Generally, it occurs a decade prior to carcinoma. The classification of dysplasias is based on the extent of the epithelial involvement. Some of the dysplasias show spontaneous regression. Nearly 30% of the severe dysplasias become invasive cancer. Tobacco use and/or consuming alcohol predominantly increase the risk of esophageal squamous cell carcinoma. Being overweight and/or reflux disease can primarily increase the risk of esophageal adenocarcinoma.

The multifocal appearance and intramural spread are common characteristics of esophageal cancer. It often spreads through the lymphatic system. Tumors involving the proximal portion of the esophagus may give metastases to the cervical lymph nodes, and tumors involving the lower portion may also give metastasis to the vicinity of the celiac artery. Cancer can infiltrate its surroundings, the pars membranacea of the trachea and the prevertebral fascia.

2. Treatment options

From a surgical point of view, early cancer means that the lesion only involves the mucosa and/or submucosa. The treatment option remains surgery for very early cancers (up to stage pT1b) while it is palliative in the case of metastatic esophageal cancer. For other cases, additional therapies, such as chemotherapy and/or radiation therapy may result in improved survival.

Regarding epidemiology, tumor biology, pathogenesis, and prognosis, the two main histological types of esophageal cancer, SCC and adenocarcinoma, are different from each other.

The perioperative mortality is higher for squamous cell cancer. It might be due to comorbidities and the localization of cancer since SCC mostly involves the upper third of the esophagus, and the postoperative mortality is significantly higher for esophageal cancer involving the proximal third. Esophageal cancer affecting the upper third and/or middle third of the esophagus recurs in a locoregional manner whereas adenocarcinoma can more often metastasize to distant sites. However, the prognosis of adenocarcinoma in an early stage is more favorable than that of SCC.

2.1. Chemoradiotherapy

The results of several randomized, phase III studies have been reported so far. Practically, a platinum-based medication is used in combination with radiation.

Morbidity and mortality are unclear regarding the use of neoadjuvant chemoradiotherapy. Some authors reported an increase in the anastomosis insufficiency and an increase in mortality, whereas others did not find an increase in mortality. A recent US study analyzed the data obtained from 1939 patients who had undergone esophagectomy. Seven hundred and eight patients received neoadjuvant therapy. They found no differences in mortality or morbidity [2]. The studies are unclear about the stage in which neoadjuvant therapy can be safely omitted. The American recommendation [3] states that neoadjuvant therapy is reasonable in the case of pT1b (>2 cm in size or dedifferentiated) whereas the European recommendation finds it reasonable only in stage T3-4 or lymph node-positive disease [4]. Chemoradiotherapy can be used

- Definitively: in inoperable cases or if the disease involves the upper third portion of the esophagus, with or without preventive, induction chemotherapy;
- In an adjuvant manner; or
- For a neoadjuvant purpose: if the patient is eligible for surgery (chemoradiotherapy, followed by surgery).

In a prospective multicenter study [5] with 186 patients with esophageal squamous cell carcinoma, three-year survival was significantly higher in patients receiving either pre-operative radiation or pre-operative chemotherapy, radiotherapy and surgery. Definitive chemoradiotherapy can be used in patients who are not surgical candidates or if the disease involves the proximal third portion of the esophagus. The main aims of care are to improve the quality of life and to maintain the patient's ability to swallow. The RTOG 8501 [6] study evaluated the benefits of concurrent chemotherapy compared to radiation therapy alone. The randomized portion of the study included 121 patients, and 61 were enrolled in the chemoradiation arm. No one had any distant metastases. Chemotherapy included the combination of continuous 5-fluorouracil (5-FU) and cisplatin. 1000 mg/m^2 of 5-FU was administered daily over 4 days during Week 1 and Week 5 of radiation treatment, as well as cisplatin at 75 mg/m^2 during the first day of Week 1 and Week 5 in combination with 50 Gy irradiation. After completion of radiation therapy, another two cycles were administered at unchanged doses. By contrast, 64 Gy irradiation was delivered as monotherapy in the other arm. Most of the patients (82%) had squamous cell carcinoma. The study proved the superiority of chemoradiotherapy over radiation therapy alone, regarding both median survival (12.5 vs. 8.9 months) and the 5-year survival (26 vs. 0%). A PRODIGE-5/ACCORD-17 study [7] included 267 patients with up to IV/A stage esophageal cancer. Cisplatin and 5-FU used in the RTOG 8501 study were compared with the administration of six cycles of FOLFOX. FOLFOX + radiation yielded results similar to those of the regimen used in the RTOG study (median PFS: 9.7 vs. 9.4 months), but it was significantly less toxic.

Primarily, the combination of taxane and platinum was assessed in the neoadjuvant setup. The most commonly used paclitaxel (50 mg/m^2) and carboplatin (AUC2, weekly over 5 weeks) were at least as efficient as the combination of platinum and 5-FU [8]; therefore, it is accepted as definitive treatment. In general, definitive chemoradiation is a choice of treatment for those patients who are not suitable for surgery or who do not consent to surgery.

Since distant metastases are present nearly in 75% of patients with locally advanced esophageal cancer, induction chemotherapy prior to chemoradiotherapy would be a rational choice. Usually, patients with locally advanced but resectable esophageal cancer were enrolled in the studies. Since there are no phase III study results, these regimens have not become recommendations. Seventy-two patients participated in the phase II, RTOG 0113 study [9]. The induction treatment included 5-FU (5 × 700 mg/m^2), cisplatin (5 × 15 mg/m^2) and paclitaxel (200 mg/m^2) or cisplatin (75 mg/m^2) and paclitaxel (175 mg/m^2), which was followed by a similar combination (5-FU + paclitaxel or cisplatin + paclitaxel) administered simultaneously with a total radiation dose of 50.4 Gy. Median survival showed no significant differences, and the toxicity was similar in both arms.

Neoadjuvant chemoradiotherapy can be used in those patients who are suitable for surgery. The method of treatment is practically identical to that of the definitive chemoradiotherapy. The aim of the treatment of inoperable patients is palliative, and the aim is to improve the proportion of operability or recovery. The studies frequently yielded contradictory results. However, based on several clinical trials and meta-analyses, neoadjuvant chemoradiotherapy proved to be superior to surgery alone in patients with locally advanced esophageal cancer. A significant survival benefit was found in the CROSS study [10] in which 366 patients with potentially resectable esophageal or gastroesophageal junction cancer were randomized to get either preoperative chemoradiotherapy (50 mg/m^2 paclitaxel a week + carboplatin AUC2, concurrent radiotherapy with a total dose of 41.4 Gy over 5 weeks) or surgery alone. Patients tolerated the combined treatment well. There were no significant differences in mortality or morbidity. The complete resection rate was 92 vs. 69% in favor of the combined treatment, and the complete pathological remission (pCR) ratio was 29% in patients receiving chemoradiotherapy. There was a significant difference in median overall survival (preoperative chemoradiotherapy followed by surgery vs. surgery alone: 49.4 vs. 24.0 months).

In the FFCD 9901 study [11], the efficacy of preoperative chemoradiotherapy was evaluated in patients with small-sized, resectable tumors. 195 patients with stage I or II disease were randomized into the preoperative chemoradiation arm (two cycles of 5-FU at 800 m/m^2 daily at Days 1–4 and 29–32, plus cisplatin at 75 mg/m^2 at Day 1 or Day 2 of the cycle, in both cycles, plus a total dose of 45 Gy concurrent radiation) or the surgery alone arm. During this study with a median follow-up of 93.6 months, there were no significant differences in the 3-year survival. No significant survival benefits were noted in any of the subgroups. Based on these data, the combined treatment may not result in any survival benefit.

Numerous meta-analyses have dealt with the comparison of the effects on survival regarding the trimodal treatment or surgery alone. One of the latest studies was published by Sjoquist and his colleagues [12]. It includes the twelve most significant neoadjuvant chemoradiation studies. The reducing effect of neoadjuvant chemoradiotherapy on mortality proved to be significant, which led to an absolute survival benefit of 8.7% after two years. It was independent of the histologic type of the tumor, and it was not associated with increased perioperative mortality, either.

In addition to the conventional cisplatin + 5-FU therapy, adding paclitaxel to platinum has become more popular lately. Results of ten studies were analyzed in another meta-analysis, and a comparison was made between the efficacy of paclitaxel together with platinum and the efficacy of platinum together with 5-FU. The analysis proved the benefit provided by neoadjuvant chemoradiation therapy over both combinations. The risk of mortality was significantly reduced with both chemotherapy combinations, but the benefit was more pronounced in the taxane arm. However, it was only statistically significant in the case of squamous cell cancer [8]. Some small-sized studies have found the combination of docetaxel and platinum effective [13, 14].

Based on the consequent results of several clinical studies, the response to perioperative treatment, especially the pCR, is an important indicator of better overall survival. Thus, intensification of the perioperative treatment could be a potential approach. Based on the results of 22 studies, survival of those patients who achieved pCR as a result of treatment was 2–3 times longer compared to those patients who had residual cancer in the resection specimen obtained via surgery following neoadjuvant chemoradiotherapy. During the intensification of neoadjuvant treatments, the employments of chemotherapy prior to chemoradiation, as well as the increase of the number of the agents have been studied. According to the INT0123 study, radiation dose intensification resulted in no improvement in either the survival or the local control [15].

Some work was conducted in relation to the non-surgical treatment options of patients with squamous cell carcinoma of the esophagus. Trimodal therapy (chemoradiotherapy followed by surgery) was compared with chemoradiotherapy by Stahl et al. and in the FFCD 9102 study. Stahl et al. [16] enrolled 172 patients. Patients received three cycles of bolus 5-FU, leucovorin, etoposide, cisplatin (FLEP) followed by chemoradiotherapy including a total dose of 40 Gy irradiation and cisplatin and etoposide chemotherapy. Patients then underwent either observation or surgery. In the surgery arm, 62 out of 86 patients underwent surgery. However, there were no significant differences in overall survival. The two-year progression-free survival was more beneficial for those patients who had undergone surgery (64.3 vs. 40.7%). Notably, both the radiation dose and the intensity of chemotherapy were lower than those used in conventional treatments. In the FFCD 9102 study [17], 259 patients with locally advanced, resectable SCC were randomized into two arms following low-dose chemoradiotherapy. If a therapeutic response was noted after the induction treatment, surgery was performed or chemoradiotherapy was completed. No significant differences were found in overall survival between the two treatment groups. However, the 3-month mortality was significantly higher ($p = 0.002$) in the surgery arm (9.3 vs. 0.8%).

Little is known about the results of the nonsurgical treatment of patients with adenocarcinoma. Based on a retrospective analysis of the results of 276 patients treated with definitive chemoradiotherapy for esophageal adenocarcinoma at the university of texas MD Anderson cancer center [18]. After a median follow-up of 54.3 months, 33.3% of the patients never had a relapse. Local relapse was present in 51% of the patients, and distant dissemination was detected in 43.5% of the patients.

There are not enough phase III results in relation to adjuvant chemoradiation. In a retrospective study by Bedard et al. [19], data of 38 patients who had undergone surgery for node-positive esophageal cancer, had received postoperative adjuvant chemoradiation (concurrent or sequential radiation therapy plus cisplatin and 5-FU ± epirubicin) were compared with data of patients who had undergone surgery only. Both the local control and median survival proved to be better in patients receiving adjuvant treatment, and so did overall survival. In another retrospective analysis [20], benefits of adjuvant chemoradiation were evaluated in 304 patients who had undergone surgery for node-positive esophageal squamous cell cancer. Based on the data, both the 5-year overall survival and the disease control proved significantly better in patients who had also received chemotherapy in addition to radiotherapy. According to a prospective study [21] that evaluated chemoradiation vs. chemotherapy and included 45 patients, neither survival benefit nor improved locoregional control was shown in the chemoradiation treatment arm relative to chemotherapy alone (cisplatin + 5-FU over 5 weeks plus 50 Gy of irradiation over 5 weeks vs. cisplatin + 5-FU over 5 weeks).

2.1.1. Neoadjuvant chemotherapy

Eight hundred and two patients with either SCC or adenocarcinoma were randomized in the MRC OEO2 study [22]. Patients received either two cycles of cisplatin + 5-FU preoperatively or underwent surgery primarily. The 5-year overall survival was 23 vs. 17% in favor of the neoadjuvant treatment regimen. In Sjoquist's meta-analysis, data of 1981 patients were assessed. Nine neoadjuvant chemotherapies were compared to surgery alone [12]. Chemotherapy reduced mortality in the entire patient population receiving neoadjuvant chemotherapy. It was significant in patients with adenocarcinoma. Based on these, neoadjuvant chemotherapy seems to be superior to surgery alone.

It is unclear whether neoadjuvant chemotherapy can be an alternative to neoadjuvant chemoradiation therapy. Stahl et al. [23] enrolled 119 patients with adenocarcinoma involving the lower third portion of the esophagus or the gastroesophageal junction. In one of the arms, patients received 15 weeks of chemotherapy (cisplatin + leucovorin + continuous 5-FU) followed by surgery. In the other arm, 12 weeks of chemotherapy were followed by concurrent chemoradiation therapy (low-dose radiation therapy and concurrent cisplatin + etoposide) over 3 weeks, and surgery was then performed. The ratio of pCR was significantly higher in the arm that included chemoradiation therapy (2 vs. 15.6%). However, there were no significant differences in median survival and the 3-year overall survival between the two treatment arms. Burmeister et al. [24] received similar results when they evaluated 75 patients with adenocarcinoma. Regarding pCR and R1 resection, chemoradiotherapy was significantly more beneficial, but there were no significant differences in median survival.

Briefly, chemotherapy can be employed as part of chemoradiation, in a neoadjuvant manner, in an adjuvant manner, or as palliation in metastatic disease.

3. Brachytherapy of esophageal cancer

The results in a large cohort of patients indicated that HDR brachytherapy alone was an effective method for the palliation of advanced esophageal cancer [25]. Similar long-term results were reported in favor of treatments involving concurrent chemoradiotherapy followed by HDR brachytherapy [26]. Although brachytherapy was found to be preferable, there are studies (such as Refs. [27, 28]) suggesting the stent placement may play an important role for the palliation of disease. In that case, the prognostic models were used as evidence-based tools in decision making. However, the health-related life quality was reported to be improved in patients treated with the HDR brachytherapy. Recent studies suggested the usage of Californium-252 neutron brachytherapy combined with EBRT for esophageal cancer. The treatment resulted in favorable local control and long-term survival rates with tolerable side effects [29]. Patient selection, timing of brachytherapy and dose specifications were well documented [30–32]. Clinicians continue to urge caution in using brachytherapy treatment techniques since severe toxicity can occur post treatment [15, 26, 30]. Therefore, the addition of brachytherapy, with consequently high surface doses, should be limited to well-selected patients [33].

For that reason, the clinical implementation and accuracy in dose delivery is crucial for favorable treatment outcomes. The radiation dose is delivered using esophageal transoral or transnasal applicators with an external diameter of 0.6–1 cm. Ideally, the single channel applicator needs to be placed centrally in the lumen of the esophagus; however, there exists a possibility that the applicator will be closer to one side of the lumen, delivering a larger dose to the epithelium, lamina propria and muscularis mucosa, resulting in local esophageal complications. In those cases, stricture formation, fistula and esophageal ulceration are the common late toxicities of HDR brachytherapy [34]. A possible difference in the delivered dose is caused by disagreements in the choice of the dose point (i.e. mucosal surface or certain distance from the central line of the applicator) in various institutions, as reported in Ref. [35]. For instance, it was reported in the long-term experience with esophageal brachytherapy treatment [36] that radiation was delivered at a level of 5 mm below the surface of the mucosa. However, no correlation was found between the post-treatment complications and the diameter of the brachytherapy applicator [37]. In most of the HDR brachytherapy treatments, 3D treatment plans were generated using computed tomography (CT) images; however, magnetic resonance imaging (MRI) can be used to assist the localization of the tumor and the applicator [38]. The treatment planning for the esophageal cancer patient is performed using the TG-43 formalism [39], since the dose calculation accuracy of the TPS was confirmed in a homogeneous medium [40].

Overall, this HDR treatment is demonstrated to be well-tolerated and effective for superficial primary and recurrent esophageal cancer in inoperable patients [41, 42]. The authors concluded that dose escalation with larger diameter applicators may allow for improved therapeutic coverage without exceeding the organs ate risk tolerances [43]. The latest research in the combined approach (EBRT and HDR) to palliation in esophageal cancer together with the review of the current techniques is reported in Refs. [44, 45].

3.1. Clinical implementation

To decrease the dose to the organs at risk in the upper gastrointestinal region a novel disposable brachytherapy transoral balloon centering esophageal applicator (BCEA) with five independently inflatable balloons was developed [44]. The complete treatment process for this applicator consisted of three principal steps: pre-treatment preparation, treatment planning and treatment delivery (**Figure 1**). This applicator allows for the central placement of the radioactive source during treatment. The BCEA allows for the treatments outside the balloon region with the constraint where the BCEA becomes similar to the standard esophageal applicator (EA).

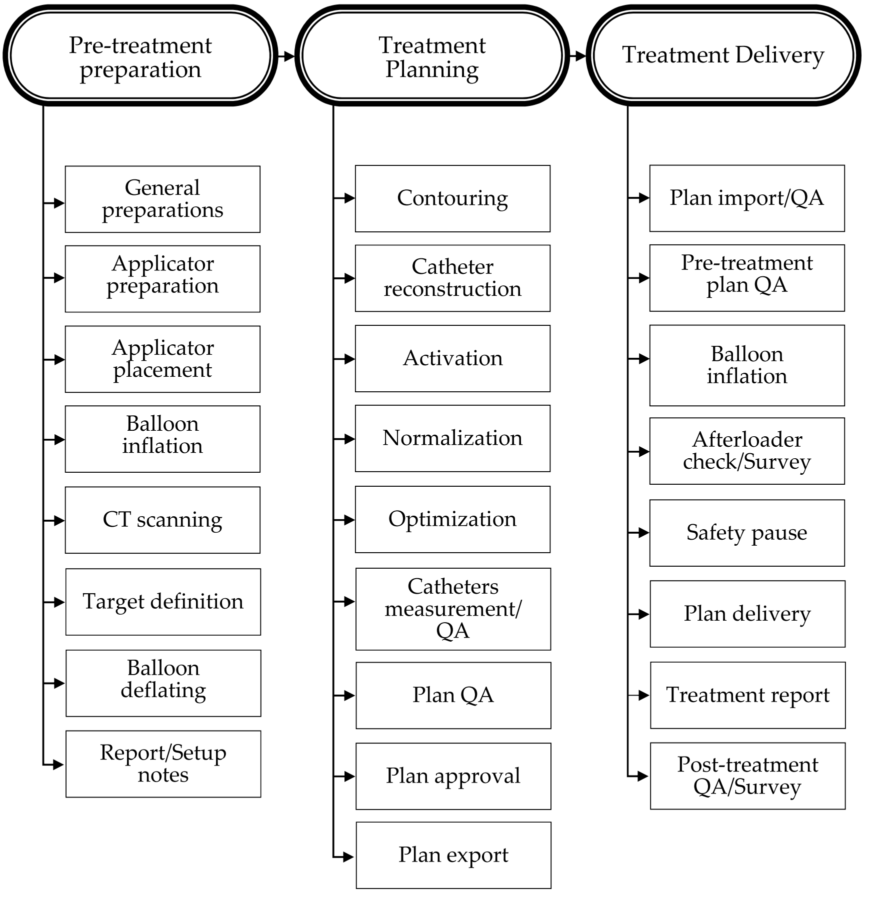

Figure 1. The detailed process map of the treatment was developed for improved treatment plan generation and quality assurance of the process.

The experience in the treatment of esophageal cancer using a standard intraluminal esophageal applicator (EA) was summarized in Ref. [45]. Unlike with the transnasal insertion (EA) where the endoscope would be placed via the anesthetized nose past turbinates and nasopharynx behind the larynx and into the esophagus, the BCEA is placed transorally.

3.2. Treatment planning and delivery

The BCEA positions the catheter centrally when the balloons are inflated. Due to that fact, the treatment plan can be additionally optimized (not the case for the standard EA) for improved dose distribution and conformality. The treatment length was defined as a pretreatment tumor length with 1–2 cm distal and proximal margin determined by pretreatment imaging and confirmed by the CT images.

The prescription dose is usually planned to be delivered to the diameter of 1 cm with respect to the central catheter with an additional optimization to avoid the critical anatomical structures such as the heart, lung, pharyngeal constrictor and spine. The dose calculation is performed using the TG-43 formalism that includes the anisotropy corrections. With the standard EA, the dose point is defined at the mucosal surface or a certain distance from the central line of the applicator with identical dwell times along the treatment length. This was mostly done to minimize the uncertainties in dose delivery related to the positioning of the EA inside the esophagus. In standard approach when EA is used the dose optimization outside the balloon region should be avoided due to the complicated position reproducibility. **Figure 2** shows the differences in the treatment plans between the EA and BCEA.

The centrally placed catheter inside the esophagus lumen resulted in enhanced dose distribution and reproducibility in multi fractional treatment (**Figure 2**). The position of the applicator and the balloon diameters can be verified before the treatments using the planning CT images and the CT images obtained prior to each fraction. Three methods can be used to verify the

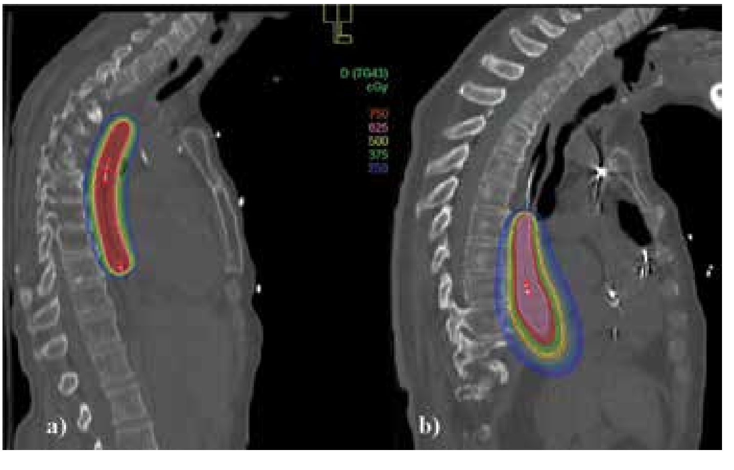

Figure 2. Sagittal images show: (a) the non-optimized plan using the EA and (b) optimized dose distribution achieved with the BCEA.

proper positioning of the BCEA prior to each treatment: (a) using an external marker to verify the length of the catheter in the patient, (b) evaluation of the position of 12 radio-opaque markers on the exterior side of the catheter in the CT images, and (c) measurements of the diameters of the balloons on CT images after inflation to confirm that they were properly inflated.

4. Conclusion

In this chapter, various aspects of esophageal cancers were disused such as histology, predisposing factors and treatment options. It was found that the moderate dose of EBRT and HDR brachytherapy could give a better local response than EBRT alone. Therefore, the brachytherapy of esophageal cancer was elaborated in more detail.

Classically, one of the limitations for the deployment of esophageal brachytherapy has been the difficulties associated with the placement and tolerance of the transnasal applicator [44]. The common adverse effects included significant pain on placement and for the duration of its indwelling. Nasal bleeding, often significant, can be seen from both the scope and catheter placement. There is often the need of significant pain medicine to tolerate this procedure. These effects are pronounced if the applicator is kept in place for an extended period of time.

Long-term toxicities and the correlation between the formation of a fistula or ulceration and the novel design of the BCEA are the topics that can be additionally investigated using the data of more patients treated with the novel BCEA and longer follow-up. Due to the limited number of patients, it is not yet possible to conclude if the patients benefit from the treatment using the centrally placed applicator. Furthermore, due to the provision to additionally optimize the dose, there exists a possibility of dose escalations for certain patients, depending on their anatomy and the spread of disease. The initial implementation of this applicator required strict and careful testing, especially in the determination of the accurate treatment length that would allow the radioactive source to be sent to the most distal position (first dwell position). Multiple tests and an interobserver agreement are required since the inaccurate results of this test can potentially offset the whole treatment, causing adverse events. Therefore, the treatment length and BCEA applicator positioning should be evaluated before each fraction.

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Chapter 5

Lymph Node Dissection along the Recurrent Laryngeal Nerve in Video-Assisted Thoracoscopic Surgery (VATSE) for Esophageal Squamous Cell Carcinoma

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69524

Abstract

Esophageal carcinoma is the ninth most common cancer in the world, which is frequently seen in Asia and east Africa. Around 80% of all cases occurred in less-developed regions. Two major histological subtypes of esophageal carcinoma, adenocarcinoma and squamous cell carcinoma, are known to differ greatly in terms of risk factor, epidemiology, male to female ratios, and incidence. Lymph node metastasis is a crucial factor in staging and prognosis is associated with surgical treatment and a major lymphatic chain into the neck. Esophageal adenocarcinoma (EAC) is mainly detected at the lower third of the thoracic esophagus or esophago-gastric-junction (EGJ) and metastasizes mainly to lymph nodes of the lesser sac, celiac regions and lower mediastinal. Esophageal squamous cell carcinoma (ESCC) has a predilection for metastasis to the lymph nodes of the cervical region including recurrent laryngeal nerve (RLN) on both sides. Lymph node dissection is vital yet difficult, left-side lymph node dissection especially requires expertise. There are some reports on lymph node dissection in the prone position by video-assisted thoracoscopic surgery of the esophagus (VATS-E) along the left RLN in Japan and China. We also introduce a stripping method for lymph node dissection in this site.

Keywords: recurrent laryngeal nerve, lymph node dissection, video-assisted thoracoscopic surgery (VATS-E)

1. Introduction

Esophageal carcinoma is strongly invasive and is accompanied by numerous malignant tumors. It is mainly seen in Asia and East Africa. In the eastern countries, especially in Japan, extended lymph node dissection, including the abdominal, upper, middle, lower mediastinal, and occasionally cervical lymph nodes, is suggested as a standard surgical method because systematic dissection of metastatic lymph nodes is thought to improve survival and lead to cure.

Consequently, recommending complete lymphadenectomy of the upper mediastinum is an essential component in radical esophagectomy for esophageal squamous cell carcinoma (ESCC). Three-field lymphadenectomy (3FL) is the ultimate surgical procedure in the pursuit of complete lymph node dissection for thoracic esophageal cancer. However, lymph node dissection along the recurrent laryngeal nerve (RLN) is difficult because severance of nerves by electrical devices can easily lead to paralysis [1, 2].

The prone position provides better visualization in the subaortic arch and subcarinal and supraphrenic regions, but the working space in the left upper mediastinum for dissecting the lymph nodes along the left recurrent laryngeal nerve is limited. Some investigators, including us, have shown how to obtain a good operative field in the upper mediastinum for lymph adenectomy. Osugi reported that tracheobronchus must be retracted ventrally to visualize the left side of the trachea and developed the retractor that provides exposure of the entire mediastinum and esophagus in left lateral position [3]. In eastern countries, surgeons also describe lymphadenectomy along the left recurrent laryngeal nerve, but few surgeons in western countries have discussed lymphadenectomy of esophageal adenocarcinoma (EAC). Here, we describe differences in lymph node metastasis between ESCC and EAC and procedures for lymph node dissection along the recurrent laryngeal nerve in ESCC.

2. Etiological differences between esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC)

Esophageal carcinoma is seen in two major histological subtypes: adenocarcinoma and squamous cell carcinoma (SCC). These subtypes are very different in terms of risk factors and epidemiology. According to GLOBOCAN 2012, there were an estimated 400,000 cases of ESCC and 50,000 cases of EAC of the esophagus in 2012 worldwide [4].

2.1. Global incidence of ESCC

In 2012, the global incidence of ESCC was 5.2 per 100,000 people. Most affected regions were located in Eastern and South-East Asia, followed by sub-Saharan Africa and Central Asia [4]. About 80% of global ESCC cases occur in Central and South-East Asian regions. China alone provided more than 50% of the global cases. Areas of high incidence of ESCC have been identified in Northern Iran, Central Asia, and China (together forming the so-called ”esophageal cancer belt”) as well as parts of Eastern Africa. ESCC is more common and the rate of ESCC is about 95% in Japan [3].

2.2. Risk factor of ESCC

Generally, chronic inflammation of the esophageal mucosa is postulated to increase the risk of ESCC. Two major risk factors are smoking and alcohol consumption, which have been found to account for more than 75% of all SCC cases in high-income countries [5]. On the other hand, frequent consumption of extremely hot beverages is a common risk factor for ESCC in less-developed regions [4]. Consumption of hot mate drinks in Latin America and hot beverages in Southern China are associated with the risk of ESCC [4, 5].

In Iran, opium use has been found to increase mortality from esophageal cancer by 50%. High-incidence areas in Africa suggest that smoking, occupational exposures and nutritional deficiencies may be responsible for the high burden of ESCC [4].

Alcohol drinking is a well-established risk factor for esophageal cancer. International Agency for Research on Cancer (IARC) referred to acetaldehyde, an oxidative metabolite of ethanol, as a potential causative agent behind alcohol-induced carcinogenesis based on evidence of interaction between alcohol consumption and acetaldehyde dehydrogenase (ALDH2) enzyme gene polymorphisms [6, 7]. Oze et al. showed that acetaldehyde dehydrogenase Glu504Lys polymorphism had strong effect modification with alcohol drinking and concluded that there is convincing evidence that alcohol drinking increases the risk of esophageal cancer in the Japanese population [8]. Half of the Japanese population is heterozygous or homozygous for the *2 allele of ALDH2, showing respectively, peak blood acetaldehyde concentrations in post-alcohol consumption 6- and 19-fold higher than homozygous wide-type individuals [9]. As a result, ALDH2*2/*2 homozygous carriers show facial flushing and nausea after alcohol consumption that deters them from drinking, whereas heterozygotes exhibit less severe reactions [9]. Fang et al. indicated that individuals heterozygous for the *2 variant allele of aldehyde dehydrogenase 2 (ALDH2*1/*2) frequently detected in Asia had an increased risk of esophageal cancer, especially among heavy drinkers, because inactive ALDH2 fails to metabolize acetaldehyde rapidly, leading to excessive accumulation of acetaldehyde in blood and repeated high exposure to acetaldehyde after drinking. Drinking clearly modifies the effect of ALDH2 on esophageal cancer risk in Asians [6].

2.3. Global incidence of EAC

The global incidence of EAC is 0.7 per 100,000 people. Highest incidence rates by region were found in Northern and Western Europe, North America, and Oceania [4]. On the national level, the highest rates were seen in the UK, the Netherlands, Ireland, Iceland, and New Zealand. The burden of AC is the highest in Northern and Western Europe, North America, and Oceania, accounting for 46% of all global AC cases [4, 10, 11].

2.4. Risk factor of EAC

The strongest known risk factor for EAC is gastroesophageal reflux disease and its more severe manifestation, Barrett's esophagus (BE). Obesity promotes the development of gastroesophageal reflux and also acts as an independent risk factor for EAC.

In North America and Northern and Western Europe, prevalence of *Helicobacter pylori* (H pylori) infection is among the lowest and incidence of EAC is higher [4, 10, 11].

Helicobacter pylori (H pylori) lowers gastric acid secretion and decreases gastric esophageal reflux [10, 11]. In more recent years, prevalence of the latter has leveled out in high-prevalence countries such as the Netherlands and the UK [4].

3. Clinical difference between EAC and ESCC

3.1. Location of ESCC and EAC

In 50–60% of cases, ESCC is located in the middle third thoracic esophagus in Thailand, Iran, and Japan [3, 12, 13, 14]. About 60% of SCCs is also located in the middle third of the esophagus in Iran. Several studies have found that ESCC was most commonly located in the lower third of the esophagus, such as studies conducted in Ghana [15].

In 80% of cases, EAC is located at the gastroesophageal junction (GEJ) and 20% in the lower third thoracic esophagus. This entity is capable of producing EAC directly or, more commonly, through an intermediate pre-neoplastic lesion or Barrett's esophagus (BE). BE is a pre-malignant lesion that develops in 6–14% of patients with Gastroesohageal reflux disease (GERD), of which approximately 0.5–1% will develop EAC [10, 11]. Increased incidence of BE in the past 30 years correlates with an increased incidence of EAC during the same period.

4. Clinical difference of lymph node metastasis between ESCC and EAC

4.1. Lymph node metastasis of ESCC

Udagawa et al. showed that it was necessary to dissect the cervical lymph nodes, particularly for tumors located in the upper and middle thoracic esophagus [2]. Bilateral cervical paraesophageal node dissection is predominantly effective and the inclusion of these stations in the regional lymph nodes is justified in the 7th TNM classification. The lower jugular or supraclavicular region lymph nodes are also important. Abdominal lymph node dissection is also effective, but the effectiveness is limited in upper esophageal cancer. The statistical efficacy index (EI) of individual lymph node stations according to the main tumor location, a more precise modification of the range of lymph node dissection is possible. Although mediastinal nodes are important in general, not all are located in the esophageal drainage area. Some specific stations such as pretracheal, left tracheobronchial, and supradiaphragmatic show least efficacy by dissection. The mediastinal node stations can be re-arranged such as recurrent laryngeal, paraesophageal, posterior mediastinal, subcarinal, and subbronchial in order, according to EI. The number of metastatic lymph nodes may be a better prognostic factor than Japanese N grading. The Japanese N-grouping seems to be more efficient for predicting of the radical and safe operation. It is difficult to detect lymph node metastasis clinically. Japanese N-grouping may be also more available in stage assessment because a single obvious distant lymph node metastasis in Japanese N-group can correctly identify a higher staging. Japanese Surgeons are afraid that discussion about lymph node dissection with precision is no longer possible if meticulous node grouping based on detailed data of lymph node stations is once discontinued.

Ma et al. stated that 3FL improves overall survival rate but has more complications. Because of the high heterogeneity among outcomes, definite conclusions are difficult to draw [16].

4.2. Lymph node metastasis of EAC

Sepesi et al. reported 72% of patients presented with clinically involved lymph nodes showed metastasis in the lesser sac (perigastric/perihepatic) [17]. However, 11% of patients had metastatic lymph nodes located at the celiac artery, and 10% had nodal disease in the paratracheal region. Ninety-eight patients demonstrated clinical metastatic involvement in one or two nodal basins (example: perigastric and paratracheal); only about 2% of patients presented nodal disease in three nodal basins. Feith et al. reported the prevalence and number of lymph node metastases according to pT category in patients with primary resected Barrett's carcinoma. A strong correlation between the pT category and the presence and the number of lymph node metastases was detected [18]. Lymph node metastases in more than 95%of the patients was detected in the lower posterior mediastinum, in the bilateral paracardiac region, or in the region of lesser curvature and left gastric artery of the abdomen. Prevalence of lymph node metastases at the various topographic locations in relation to the T category of the underlying Barrett's carcinoma is shown. As T category increases, prevalence of regional lymph node metastases also markedly increases. Lymph node metastases to more distant locations, such as the tracheal bifurcation region, the proximal mediastinum, or celiac axis, lagged behind and were common only in patients with more advanced primary tumors. This suggests that lymphatic spread occurs in an orderly fashion. Patients who had many lymph nodes metastasis had distant lymph node metastasis in the upper mediastinum and tracheal bifurcation area that can be reached by a transthoracic approach [19]. According to an increasing number of lymph nodes metastasis, positive lymph node metastasis in the upper mediastinum and carinal region also increased. Prevalence of lymph node metastases at the celiac axis was also detected with increasing number of lymph nodes metastasis. There was significantly frequent lymph nodes metastasis in the upper mediastinal, carinal or celiac regions among patients with more than three positive regional nodes. Overall, skipping of regional lymph node stations, positive distant nodes in the absence of positive regional nodes, was seen in less than 5% of the patients.

Yamashita et al. reported clinical records of 2807 EGJ carcinoma patients without preoperative therapy in Japan [20]. There are obvious unbalances in terms of lymph node dissection rate according to histology and the main tumor location. Lymph nodes metastasis frequently involved abdominal lymph nodes. Lymph nodes at the right and left cardia, lesser curvature and along the left gastric artery were especially metastasized. Lymph nodes along the greater curvature of the stomach were not frequently metastatic, and advantage of dissection seemed unlikely. Lower mediastinal node dissection may contribute to improved survival for patients with esophagus-predominant EGJ carcinoma. However, due to low dissection rates for nodes of the middle and upper mediastinum, no conclusive results have been obtained regarding the optimal extent of nodal dissection in this region.

5. Lymph node metastasis along the recurrent laryngeal nerve

Extensive lymphadenectomy with esophagectomy for esophageal carcinoma improves the prognosis in Japan. In particular, lymph nodes along the RLN are considered as significantly important lymph nodes those are recommended to be completely dissected. However, lymph node along the RLN dissection complicates high morbidity and mortality. Udagawa et al. showed lymph node metastasis along the rt. RLN and cervical paraesophageal at a rate of 31.9, 22.2%, 19, 13.9%, and 14.7, 12.4% of upper, middle, and lower thoracic esophagus, respectively. Lymph node metastasis along the lt. RLN and cervical paraesophageal was found at a rate of 19.1, 20.1%, 14.1, 8.3%, and 8.1, 5% of upper, middle, and lower thoracic esophagus in Japan, respectively [2]. Ye et al. reported that the recurrent laryngeal nerve lymph node metastasis from esophageal carcinoma is detected at the rate of 34.2% in China [21]. Lymph node metastasis along the recurrent laryngeal nerve was detected, and the rate of lymph node metastasis was 23.4%. The rate of rt. RLN lymph node metastasis was 20.8%, which was slightly higher than the rate of lt. RLN lymph node metastasis which had a rate of 15.8%.

5.1. ESCC

In ESCC, lymph node metastasis is possible to occur in the neck, mediastinum, and abdomen. The location of RLN lymph node is from the upper mediastinum and to the cervical region, where lymph node metastasis is frequently detected in thoracic ESCC. Early, initial and micro metastasis of ESCC often occur and RLN lymph node metastasis has been regarded as an indication for three-field lymphadenectomy in the surgical treatment of ESCC. More importantly, RLN metastasis has been shown to be a strong predictor of poor prognosis in ESCC.

There are many reports about lymph node metastasis along the recurrent laryngeal nerve in Asia. In Japan, Igaki et al. reported that cervical or celiac lymph node metastasis in patients with carcinomas of the lower thoracic esophagus should be distinguished from pathologic M1 status in the UICC-TNM staging system [1].

5.2. EAC

Giacopuzzi et al. reported that in Siewert type I tumors, when standard mediastinal lymphadenectomy is performed, about half of the node-positive patients show positive nodes in mediastinal stations [22]. Specifically, upper and mid mediastinal lymph node metastases (right paratracheal, subcarinal, aortopulmonary window) were reported in up to 25% of patients. When the few studies in which cervical nodes are also removed are considered, a non-negligible incidence of metastases is detectable, but, due to the scarcity of available data and the higher complication rate of three-field dissection, this is not currently thought to be relevant in clinical practice. Mediastinal nodes are involved in about 30% of Siewert type II cases. Although most of the positive nodes occur at lower stations, the rate of metastasis detected in the upper-mid mediastinum after transthoracic esophagectomy ranges between 8 and 22% [22].

6. Lymph node dissection along the recurrent laryngeal nerve

6.1. ESCC

Surgeons in Asia, where the rate of ESCC is higher, perform lymphadenectomy along the recurrent laryngeal nerve. Udagawa et al. reported that cervical lymph node dissection had high efficacy index (EI) in upper and middle thoracic esophageal cancer but a low EI in lower esophageal cancer. Cervical lymphadenectomy for lower esophageal cancer showed some but limited efficacy only in cervical paraesophageal stations [2]. Three-field lymph node dissection may be indicated even for patients with clinical Stage I ESCC requiring surgical intervention because this surgical procedure offers possible cure by removing unsuspected lymph node metastasis. Altorki et al. also mentioned that three-field lymph node dissection with esophagectomy can involve with a low mortality and reasonable morbidity. Unsuspected metastases to the lymph nodes along the RLN and cervical region are present in 36% of patients in spite of histological tumor type or tumor location of the esophagus [23].

Osugi et al. reported that video-assisted thoracoscopic surgery (VATS), a less invasive method that preserves curability, provides comparable results to open radical esophagectomy. Palanivelu et al. demonstrated the lymph node dissection along the recurrent laryngeal nerve in prone position to be effective [24].

6.2. EAC

Lagergren et al. indicated that the extent of lymphadenectomy during surgery for esophageal carcinomas which include 83.5% adenocarcinoma may not influence 5-year all-cause or disease-specific survival [25]. These results challenge current clinical guidelines.

Feith et al. showed that a transthoracic approach followed by an extended lymph node dissection in the upper mediastinum is not recommended in patients with adenocarcinoma of the distal esophagus. Conservative surgical resection due to the virtual absence of lymph node metastasis in the upper mediastinum can cure patients with high-grade dysplasia and pT1a carcinoma. In addition systematic lymph node dissection of the lower posterior mediastinum and upper abdominal compartment can improve the prognosis in patients with more advanced tumors and a limited number of regional lymph node metastases. A transmediastinal approach with a wide splitting of the esophageal hiatus can achieve this radical lymph node dissection in the lower posterior mediastinum and upper abdominal compartment. Multimodal treatment protocols including chemotherapy and irradiation on systemic therapy are considered to be more appropriate for patients with more extensive lymph node metastases [25].

Cuscheri et al. recommended placing the patient prone to clear the posterior mediastinum, thus avoiding lung compression, but did not demonstrate lymph node dissection along the recurrent laryngeal nerve in EAC patients [26].

6.3. Lymph node dissection along the rt. recurrent laryngeal nerve

Thoracoscopic lymph node dissection along the right (rt.) recurrent laryngeal nerve has been more readily demonstrated by various authors. The rt. recurrent laryngeal nerve LN is removed as follows: the location of the right vagal nerve and the right inferior subclavian artery are confirmed. The airway behind the mediastinal pleura is opened to expose the right subclavian artery. The rt. recurrent laryngeal nerve is separated from the right vagal nerve followed by blunt dissection of the right recurrent laryngeal nerve through the vagus nerve trunk at the level of the right subclavian artery. We performed VATS-E in prone position (**Figure 1**). The surrounding LNs and fatty tissues are subsequently removed from the right recurrent laryngeal nerve [27] (**Figure 2**).

To reduce the risk of paralysis, an electric device is used to separate the nodes from the recurrent laryngeal nerve within 2 s [27].

6.4. Lymph node dissection along the lt. recurrent laryngeal nerve

Lymph nodes along RLNs are thought to be significantly involved by carcinoma cells as well as a main lymphatic chain to the neck, and complete dissection of these nodes is recommended. However, a lymphadenectomy, especially along the left RLN by thoracoscopic esophagectomy, is considered to be a burdensome step due to difficult operative exploration at the left upper mediastinum. To achieve a precise dissection of this portion, stable operative views and technical feasibility are necessary. Noshiro et al. mentioned that in their lymphadenectomy procedure along the left RLN, performing a thoracoscopic esophagectomy in the prone position had advantages compared to surgery in the left lateral decubitus position [27]. They introduced such details, during the procedure, the trachea is rolled back carefully and firmly to the right and ventrally by a grasper holding small gauze to explore the left aspect of the trachea and the left bronchus. The tissue, including the left RLN and lymph nodes, is

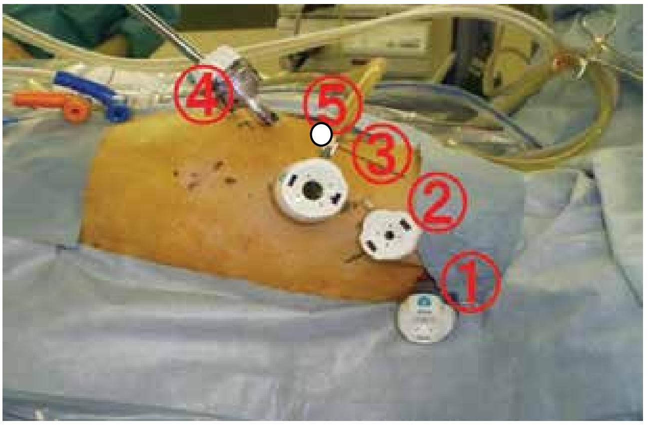

Figure 1. Port site in prone position. 3rd ICS, middle A.L.(1), 5th ICS, posterior A.L.(2), 7th ICS, posterior A.L.(3), 9th ICS, SSCL(4), 7th ICS, SSCL(5). ICS: inter costal space, AL: axillary line, SSCL: subscapular line.

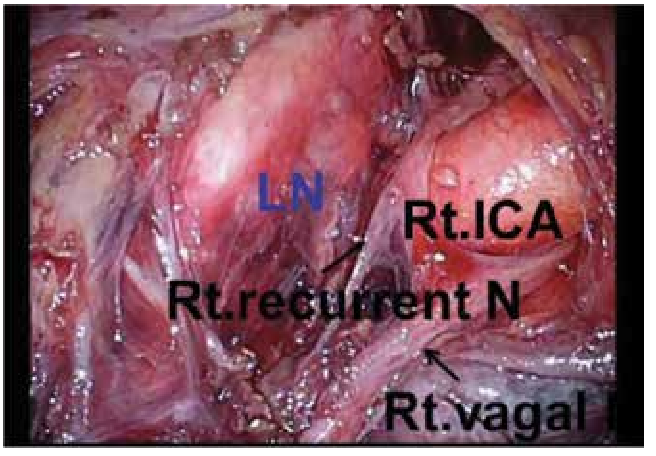

Figure 2. Lymph node dissection along the rt. RLN.

dissected sharply just along the trachea and the left bronchus to make a ventral border of dissection. Finally, the left RLN is sharply isolated from the explored tissue without using an electric device to avoid injury by electricity or heat, and the lymph nodes were consequently dissected in an en-bloc fashion accompanied with the divided thoracic duct.

However, dissecting the lymph nodes along the left RLN during VATS is challenging and requires significant technical skill, and there is limited working space in the left upper mediastinum for dissecting the lymph nodes along the left RLN and expertise in dissection is required. The technique of lymph node dissection along the lt. RLN in VATS-E has been demonstrated by some authors (**Table 1**).

We have previously reported a "Stripping method" to overcome this disadvantage in prone position [28]. Therefore, we considered stripping the esophagus toward the neck to remove the esophagus. Both the esophagus and stomach tube in the upper mediastinum are cut apart from the tumor by a linear stapler after isolating the esophagus (**Figure 3A**). The residual esophagus is stripped in the reverse direction and retracted toward the neck when the stomach

Method		Position
Stripping method	Makino et al. [28, 29]	Prone position
Bascule method	Oshikiri et al. [30]	Prone position
Suspension method	Xi et al. [31]	Prone position
Suspension method	Zheng et al. [32]	Prone position
LN dissection of hybrid position	Kaburagi et al. [33]	Hybrid position
Looping method	Lin et al. [34]	Prone position
Mediastinoscopic LN dissection	Fujiwara et al. [35]	Spine position

Table 1. Methods of lymph node dissection along the RLN.

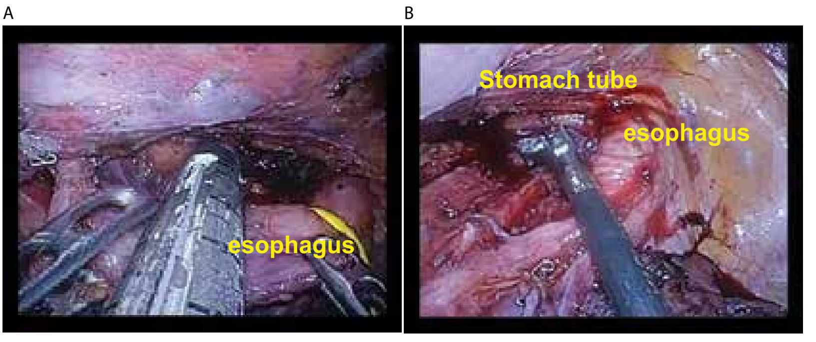

Figure 3. (A) Cutting both the esophagus and stomach tube. (B) Stripping by pulling the stomach tube.

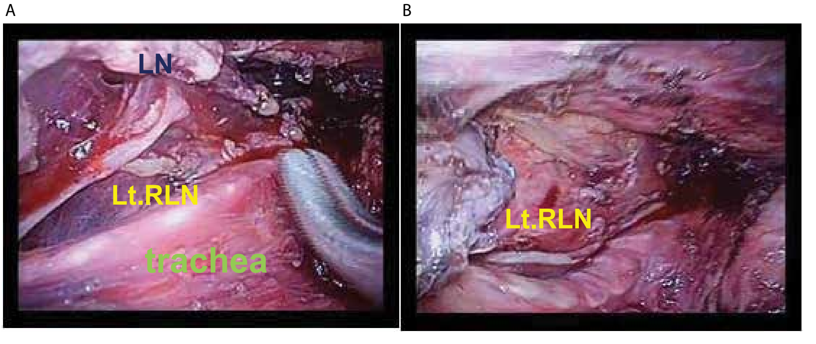

Figure 4. (A) Lymph node dissection along the lt. RLN. (B) After LN dissection along the lt. RLN.

tube is removed through the nose by anesthesiologist (**Figure 3B**). The wide operative field of left upper mediastinum is possible using this stripping technique. Lymph node dissection is performed after stripping the residual esophagus [28, 29] (**Figure 4A**). Moreover, working space is created by compressing the right main bronchus or retracting the trachea using a retractor. Lymph node and fat tissue are ablated from the left edge of the trachea, after which lymph node along the left RLN is dissected (**Figure 4B**). An electrical device is used to separate the node from the nerve, and endoscopic scissors and forceps are used during sharp dissection along the nerve. One hundred patients with esophageal carcinomas underwent VATS-E (27 in left lateral position and 73 in prone position). This original technique of lymphadenectomy along the left RLN has been performed in 54 patients in the prone position VATS-E. The rate of transient recurrent laryngeal nerve palsy is 17.2%, but permanent palsy is only 1.2% [29].

Oshikiri et al. developed the "Bascule method" where the proximal portion of the divided esophagus and tissue that includes the left RLN and lymph nodes are drawn through a gap between the vertebral body and the right scapula [30]. The membranous portion between the esophagus and the trachea like the esophageal mesenteriolum is ablated by traction of the tissue including the left RLN and lymph nodes along the left RLN by the proximal esophagus. The lymph node along the left RLN is distinguished from the left RLN and the tracheoesophageal artery on the posterior side of the left RLN can be detected and easily cut by this traction technique. The esophageal mesenteriolum is possibly drawn by taping of the entire length of the undivided esophagus. However, there is a limit to the amount of retraction. Division of the esophagus increases the amount of retraction possible, allowing for further drawing and development of the operative field.

Xi et al. and Zheng et al. showed an esophageal suspension method in scavenging peripheral lymph nodes of the lt. RLN. In this method, a traction line is used to suspend the incompletely stripped esophagus [31, 32]. Tissues including the left RLN and lymph nodes were extended, which improved operative exposure. Tissue is released in the area close to the trachea and left main bronchus in order to dissect the ventral and cranial borders. The left RLN and LNs are easily recognizable. The lt. RLN to the thyroid gland and the lymph nodes along the left RLN are separated using endoscopic scissors, keeping the remaining lymph nodes attached to the esophagus.

Kaburagi et al. demonstrated hybrid position method that radical lymphadenectomy along the bilateral recurrent laryngeal nerves was performed in the left lateral decubitus position because this approach was superior for lymphadenectomy in the region. Thoracoscopic esophagectomy and other lymphadenectomy were provided in the middle to lower mediastinum in prone position [33].

Lin et al. reported that after looping the esophagus and fixation with a clip, the exposed thorax part of the thread is pulled up by the assistant to lift esophagus [34]. The left RLN is then exposed and separated in the space between lifted esophagus and the trachea. Scissor and isolating forceps are preferred during separation due to safety concerns. During subsequent mobilization of the esophagus and dissection of left RLN lymph nodes, the assistant uses the grasping forceps to compress the trachea so as to better expose the space between esophagus and trachea.

Fujiwara et al. reported that the lymph nodes along the left RLN could be separated from the left RLN trunk using endoscopic scissors under a mediastinoscope, with the nodes remaining attached to the esophagus [35]. First, the nerve trunk is exposed along the anterior plane, then, the lymph nodes are retracted to the left, through beneath the nerve trunk, and separated by dividing the attachment to the nerve trunk. Finally, the subaortic arch lymph nodes are dissected by dividing the attachment to the nerve trunk.

To avoid injury to the lt. RLN by electricity or heat, an electric device should not be used. Wong et al. demonstrated that a more aggressive and thorough nodal dissection may be possible with less concern of RLN injury by the availability of intermittent nerve mapping and continuous intraoperative nerve monitoring (CIONM) [36].

7. Conclusion

In eastern countries ESCC is common and lymph node metastasis along the RLN is frequently seen. Many surgeons in Japan, China and India perform thoracoscopic lymph node dissection along the RLN. The prone position allows for visualization of a dry and wide surgical space without the need for special assistants, but there is difficulty in lymph node dissection along the left RLN. To obtain a good and wide operating field for lymph node dissection along the left RLN, only retraction or rotation of the trachea toward the right is insufficient. With our technique, the residual esophagus can easily be pulled up to the neck after sufficient ablation. In this technique, it is not necessary to retract the esophagus with more holes or to fix the esophagus. Esophageal stripping in lymph node dissection is easier and more effective than other methods.

Lymph node dissection along the left RLN after esophageal stripping is possible in the prone position during VATS-E.

Acknowledgements

The authors like to thank Dr. Hiroshi Maruyama, Dr. Yuta Kikuchi, Dr. Koji Ueda, and Dr. Masafumi Yoshioka for their clinical support.

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Nutritional Management of Esophageal Cancer Patients

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69607

Abstract

Esophageal cancer is associated with malnutrition in the vast majority of patients. This phenomenon is partly attributed to the disease process itself, the location of the tumor and other factors, such as dysphagia which is often accentuated due to chemotherapy/radiotherapy treatment or surgical intervention. The poor nutritional status of these patients is often related to the presence of cancer cachexia, altered metabolism, and tissue wasting. Malnutrition in this patient population affects quality of life, worsens patient's tolerance to chemotherapy and accounts for lower survival. Nutritional management of these patients includes both proper nutritional assessment and support and might prevent, to a certain extent, the manifestation of malnutrition-related consequences. The purpose of this article is to review the current literature in order to focus on the etiology and diagnosis of malnutrition in esophageal cancer patients, emphasizing also on the optimal nutritional support during multimodality treatment.

Keywords: nutritional assessment, nutritional support, perioperative nutritional care, esophageal cancer

1. Introduction

Esophageal cancer is one of the most fatal cancers worldwide as it was ranked ninth for cancer incidence and sixth for cancer death in 2013. In 2013, there were 442,000 new cases of esophageal cancer and 440,000 deaths [1]. There are two main histologic subtypes of esophageal cancer: squamous cell carcinoma and adenocarcinoma, each one of them is related to several risk factors. Among them, modifiable lifestyle factors, such as alcohol consumption, tobacco use, and nutrition should be considered as key points in order to prevent esophageal cancer.

Excess alcohol consumption and consumption of hot food and beverages increase the risk of esophageal squamous cell carcinoma, whereas many components of Western type diet, such as red and processed meat increase the risk of esophageal adenocarcinoma [2–4]. Moreover, obesity, especially central type, and gastroesophageal reflux disease are risk factors toward developing esophageal adenocarcinoma [5, 6]. On the other hand, healthy dietary habits could be a shield against some types of esophageal cancer [7], while nutritional support could be beneficial for the management of these patients after cancer diagnosis.

Esophageal cancer is commonly associated with malnutrition and impaired nutritional intake. Nutritional management of these patients may differ according to the type of therapy and stage of disease, in order to alleviate symptoms, ameliorate nutritional status, and improve quality of life. Furthermore, cancer cachexia affects a great percentage of esophageal cancer patients emerging as a significant factor the multidisciplinary team should deal with [8]. Regarding the perioperative care, the proper type of feeding (i.e. enteral/parenteral nutrition (EN/PN), immunonutrition, oral supplements, etc.) as well as the right time of feeding is a matter of controversy due to lack of consistent evidence for patients undergoing esophagectomy [9]. Special nutritional needs in the long run are also of great significance for patients with both resectable and unresectble disease, bearing in mind that the majority of these patients strive to meet their caloric and protein needs. Considering the treatment approach, nutritional screening and assessment leads to early detection of malnourished patients in need of nutritional support. Taking into account patient's specific needs helps to choose the most suitable routes of delivering nutritional support (nutritional counseling and artificial nutrition). Personalized nutritional support could modify poor nutritional status resulting in reduced postoperative complications and improved survival. Moreover, the implementation of nutritional protocols could reduce toxicity of treatment regimens and in conjunction with nutritional monitoring could have impact on patients' daily living [10]. Therefore, nutritional therapy should be an essential part of a multidisciplinary approach in the clinical setting, in order to improve short- and long-term outcomes.

The aim of the current review is to focus on the etiology of malnutrition, review the various methods of nutritional assessment, and analyze the aspects of nutritional management of esophageal cancer patients as a fundamental part of multimodality therapy.

2. Nutritional status

2.1. Malnutrition rates and weight loss

Esophageal cancer patients often suffer from malnutrition, the manifestation of which is strongly linked to the stage of the disease and therapeutic regimens. Excessive weight loss is partly attributed to the disease process itself and is often deteriorated due to chemotherapy/radiotherapy treatment [11]. Malnutrition occurs in 60–85% of esophageal cancer patients, which is one of the highest reported rates when compared to other malignancies, such as lung, head and neck, stomach, and pancreatic cancers [12]. According to recent publications, 32% of patients who underwent esophagectomy experienced more than 10% weight loss preoperatively [13], while 90% of patients had a 5% weight loss at 3 months postoperatively [14]. It is noteworthy that in many patients weight loss persists for at least 3 years after surgical intervention [15]. Another study revealed that 43.8% of patients with esophageal cancer were underweight based on BMI values, 29.7% of patients were undernourished as indicated from anthropometric measurements and 69% had weight loss within 2 weeks before hospital admission [16]. Chemotherapy and radiotherapy affect nutritional status by promoting weight loss and muscle wasting. More specifically, malnutrition developed in 83.8% of patients after the end of radiotherapy [17] and the number of patients requiring nutritional intervention increased from 56 to 75% during induction chemotherapy [10]. These facts highlight the need of nutritional assessment at several time points in order to identify patients who are candidates for nutritional support.

2.2. Methods of nutritional assessment and impact on clinical outcome

There are various methods of nutritional assessment in the clinical setting providing clinicians with tools for the evaluation of the nutritional status and the estimation of nutritional needs of esophageal cancer patients. One commonly used criterion of malnutrition is the percentage of weight loss in a certain period of time. A weight loss of more than 5% in the previous month or more than 10% in the last 3–6 months is considered significant malnutrition [18]. One retrospective study concluded that weight loss <10% and BMI>18 kg/m^2 were significantly correlated with a better response to chemoradiotherapy, while BMI>18 kg/m^2 was predictive of survival at both univariate and multivariate analysis [19]. Other anthropometric measurements, such as mid-arm circumference and mid upper-arm muscle area can give information about the nutritional status and body composition of these patients.

Biochemical markers, such as plasma proteins are often used as nutritional markers. For instance, albumin is commonly used for the assessment of protein status, but given its long half-life (14–20 days), it has a slow response to dietary interventions and cannot detect subtle changes in nutritional status. Furthermore, albumin reflects an acute phase response and is not always a reliable marker of malnutrition [20]. However, albumin is an independent risk factor for complications after esophagectomy, since patients with hypoalbuminemia have twice the risk of postoperative infection and increased incidence of acute respiratory distress syndrome [21]. A recent review examined the association of serum albumin with postoperative complications in patients undergoing esophagectomy, suggesting that low serum albumin does increase the risk of postoperative complications, but there is still conflicting evidence regarding the prognostic value of this biomarker [22].

Other methods of nutritional assessment include questionnaires that incorporate many factors that impede adequate nutritional intake, as well as laboratory parameters, and unintentional weight loss. For example, Subjective Global Assessment (SGA), a questionnaire based on four parameters of patient's history (percentage of weight loss, changes in habitual diet, presence of significant gastrointestinal symptoms, and changes in patient's functional capacity) and three elements of their physical examination (loss of subcutaneous fat, muscle wasting, and presence of edema or ascites) is one the most commonly used tool for nutritional screening in malnourished hospital patients with cancer. SGA is strongly correlated with performance status in esophageal cancer patients [16] as well as with The Glasgow prognostic score and with complications during cancer treatment [23]. Other tools that have been studied in cancer patients is the Prognostic Nutritional Index (PNI), the Nutritional Risk Screening 2002 (NRS 2002), the Controlling Nutritional Status (CONUT) and the Nutritional Risk Index (NRI). Esophagectomized patients with a high Prognostic Nutritional Index—a tool which includes serum albumin and absolute peripheral lymphocyte count—had a higher prevalence of postoperative complications [24]. These results are in accordance with later studies, indicating that nutritional status preoperatively, expressed as PNI, was significantly related with the occurrence of severe complications and was a predictive factor for long-term survival [25, 26]. Nevertheless, Han-Geurts et al. showed that PNI was not associated with postoperative infectious complications in patients who underwent esophageal resection for malignancy [27]. NRS-2002 is recommended by the European Society for Clinical Nutrition and Metabolism as a standard tool for the assessment of surgical patients [28], but it is not tailored to esophageal cancer patients, thus limiting its prognostic value in this population. The CONUT score, which is calculated by serum albumin concentration, total peripheral lymphocyte count, and total cholesterol concentration, was developed as a screening tool for early detection of patients at risk of malnutrition [29]. Patients classified preoperatively as moderate or severe malnourished had a higher incidence of pulmonary and other severe morbidities, surgical site infections, and reoperation. Consequently, the duration of hospital stay in patients with moderate or severe malnutrition was significantly longer compared to well-nourished or slightly malnourished patients [30]. Similarly, Hirahara et al. [31] and Toyokawa et al. [32] demonstrated that CONUT was significantly associated with cancer death and poorer disease-free survival in patients with resectable esophageal squamous cell carcinoma. NRI is another tool used for the assessment of malnutrition based on serum albumin concentration and weight loss. Increased nutritional risk, derived from NRI, is associated with reduced survival in esophageal cancer patients treated with definitive chemoradiotherapy [10, 33], but is not associated with postoperative infectious complications in patients treated with esophagectomy [27]. The Geriatric Nutritional Risk Index (GNRI) is a new index recently introduced for the assessment of nutritional status of elderly patients. Patients diagnosed with poor nutritional status according to GNRI had significantly higher rate of respiratory complications after esophagectomy and gastric tube reconstruction [34]. In conclusion, there are several nutrition assessment tools for esophageal cancer patients, but since many of the studies mentioned above are of retrospective nature, the gold standard for the evaluation of nutritional status in this cancer subpopulation is yet to be determined (**Table 1**).

Percentage of unintentional weight loss	*Biochemical markers* (albumin, prealbumin, total peripheral lymphocyte count)	*Questionnaires and indices:* SGA, NRS2002, CONUT, NRI, PNI, Glasgow Prognostic Score

Table 1. Nutritional assessment of esophageal cancer patients.

2.3. Sarcopenia and cancer cachexia

Patients with esophageal cancer often witness loss of muscle mass and/or muscle strength, a condition described as sarcopenia. Although there are many different definitions of the term sarcopenia, all of them place emphasis on the impaired physical function following decreased muscle mass [35–37]. Sarcopenia is a component of cancer cachexia, especially in advanced stage cancer patients. Cancer cachexia is a complex syndrome which combines anorexia, early satiety, weakness, anemia, inflammation, weight loss, and loss of muscle mass with or without loss of fat mass [38]. A recent study pointed out that the prevalence of cancer cachexia in advanced esophageal cancer patients was 52.9% [39]. There is lack of consensus on the definition, diagnostic criteria, and classification of cancer cachexia, but the most commonly used definition includes one of the following: Weight loss >5% over past 6 months (in absence of simple starvation); or BMI <20 and any degree of weight loss >2%; or appendicular skeletal muscle index consistent with sarcopenia (males <7.26 kg/m^2; females <5.45 kg/m^2),and any degree of weight loss >2% [40]. Furthermore, assessment of sarcopenia plays an emerging role in cancer patients owing to the fact that CT scanning is a gold standard imaging method of body composition analysis at the tissue-organ level [41]. CT scans can identify reduced muscle mass and predict negative cancer outcomes in people with abdominal malignancies, where traditional methods of assessment are less effective [42]. Handgrip strength is another method used to measure muscle strength, which is directly related to the physiologic status of the individual and reflects patient's nutritional status. It could be easily used in patient's nutritional assessment due to the fact that it is an inexpensive and not time-consuming method.

Sarcopenia and cachexia are prognostic factors for surgical complications, decreased survival, and poor response to chemotherapy. More specifically, patients with weak handgrip strength had higher risk of complications and mortality after elective esophagectomy [43]. Decreased muscle mass, assessed by preoperative computed tomography scans, seems to be an independent predictor of both overall survival (**Figure 1**) [44] and disease-free survival, as significant as tumor stage, in patients following esophagectomy [45, 46]. In addition, sarcopenic patients who underwent esophagectomy had significantly higher rate of respiratory complications compared to nonsarcopenic subjects, but there was no difference in the incidence of overall complications between the two groups [47–49]. Sarcopenia has also impact on chemotherapy outcome since decreased muscle mass is associated with dose-limiting toxicity and pathological chemotherapy response in patients receiving neoadjuvant chemotherapy [50–52]. Therefore, it is imperative to estimate patients' muscle mass not only preoperatively but also before the onset of chemotherapy, bearing in mind that sarcopenia is frequently masqued by obesity making it more difficult to define patients' needs for intervention.

2.4. Mechanisms of malnutrition

Malnutrition, as mentioned above, affects a great percentage of esophageal cancer patients. Most patients are not able to achieve a positive energy balance and in many cases, initial body weight cannot even be maintained. This is ascribed mainly to impaired metabolism and side effects caused by esophagectomy or chemotherapy/radiation treatment. Dysphagia is a very common mechanical cause of malnutrition and is accompanied by dietary changes in order to

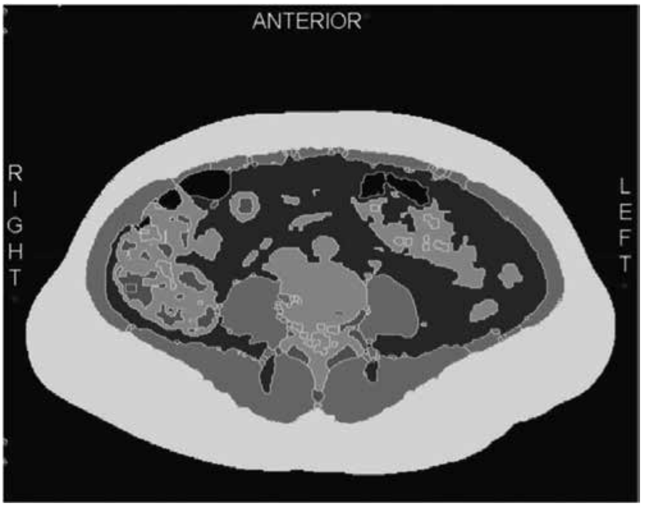

Figure 1. Example of CT scan analysis by the Slice-O-Matic software. Lumbar vertebrae 3 slice with Hounsfield units used to measure area of skeletal muscle, subcutaneous fat and visceral fat. White outer ring, subcutaneous fat; Light grey inner ring, muscle; Dark grey central area, visceral fat. Reproduced from Gibson et al. [42].

avoid foods that worsen symptoms leading to inadequate intake of calories. The surgical procedure often causes deficiencies in macronutrients and micronutrients, with the most prevailing side effects being postprandial dumping syndrome, dysphagia, anorexia, reflux, and early satiety [53–55]. Furthermore, chemotherapy affects rapidly proliferating cells preferentially and, consequently, affects the cells of the gastrointestinal tract. Chemotherapy-related causes of reduced food intake include nausea, vomiting, diarrhea, mucositis, and decreased appetite. Radiotherapy also contributes to malnutrition, and combined with chemotherapy exacerbates patients' nutritional status. Common side effects of radiotherapy include mucositis, esophagitis, odynophagia, mouth and throat soreness, and hypogeusia [56]. Tumor-related causes of malnutrition are also of great significance, but the mechanisms involved are still under investigation. Cancer-induced anorexia may result from circulating factors produced by the tumor or by the host in response to the tumor. For instance, cytokines, such as interleukins (IL) and tumor necrosis factor-alpha (TNF-α) cause anorexia [57], whereas other tumor-secreted factors promote central- and peripheral-mediated cancer cachexia. Tumor growth results in the secretion of pro-inflammatory factors that promote cachexia by signaling anorexia, muscle wasting, and white adipose tissue atrophy. Tumors also secrete both the proteolysis-inducing factor and activin, which promote skeletal muscle degradation and sarcopenia [58, 59].

Even though the mechanisms behind muscle wasting have been widely studied, less is known about the factors implicated in adipose tissue loss in cancer cachectic patients, such as lipid-mobilizing factor, as well as about the derangement in the neuroendocrine regulation of food intake and anorexia [60]. Additionally, changes in carbohydrate, lipid, and protein metabolism account for altered substrate metabolism. Changes in resting energy expenditure (REE) are considered one of the causes of nutritional depletion in cancer. In particular, measured REE by indirect calorimetry (IC) was elevated in patients with newly detected esophageal cancer, compared to healthy individuals [61]. A cross-sectional study involved 30 patients admitted with a diagnosis of squamous cell carcinoma who underwent IC before starting cancer therapy. The basal energy expenditure (BEE) was evaluated using IC and was also estimated using the Harris-Benedict Equation (HBE). The results showed that BEE of patients with squamous cell carcinoma was underestimated when using the HBE [62]. However, current evidence is inconsistent, since some studies suggest that REE is normal and is not affected by stage of disease [63–65]. Consequently, more research should be conducted in order to shed light on this controversial field.

3. Perioperative nutritional care

3.1. Enteral versus parenteral nutrition

Esophagectomy is one of the most invasive and time-consuming operations among gastrointestinal surgical procedures. It induces a strong stress response in the human body [66]. Consequently, patients' nutritional status is deteriorated after surgery, making postoperative nutritional care very important. The use of enteral nutrition (EN) postoperatively is a matter of debate, while scientific research attempts to define the role of enteral and parenteral nutrition (PN) on the clinical outcome of patients undergoing esophagectomy. Enteral feeding is considered the method of choice for the nutritional support of cancer patients with functioning gastrointestinal tract. Enteral nutrition is advantageous over parenteral nutrition for the following reasons: it provides all the necessary micro- and macronutrients in a more intact form, maintains gut mucosal integrity, inhibits the cytokine response, reduces the secretion of stress hormones, inhibits bacterial translocation, has a decreased risk of complications, and is less expensive [67]. Nevertheless, enteral nutrition is often avoided in order to minimize strain to the anastomoses, and reduce the risk of postoperatively impaired gastrointestinal motility. Another concern involves the return of gut motility or peristalsis and the ability of the gut to absorb nutrients. Surgical advances have increased the integrity of all anastomoses, making early oral enteral feeding after surgery a feasible option.

A randomized control trial investigated the outcomes of PN or EN after thoracoscopic esophagectomy. The rate of weight loss at postoperative day (POD) 14 was significantly lower in the EN group than in the PN group. Prealbumin levels at POD 10 showed no differences between the two groups. However, the incidence of postoperative pneumonia was higher in the PN group than in the EN group [68]. The results of another randomized clinical trial showed that there was no significant difference between EN and PN groups in terms of postoperative serum albumin, prealbumin, or transferrin. However, complement component 3 (C3) and 4 (C4) levels were significantly higher in the EN group compared with the PN group, while C-reactive protein level was significantly lower in the enteral feeding group. Bowel movements were restored sooner and costs of treatment were lower in the EN group. Postoperative complications did not differ significantly between the two groups [69]. Results from a recent meta-analysis of 10 randomized controlled trials concerning cancer patients following esophagectomy indicated that early postoperative enteral nutrition could significantly decrease pulmonary complications and anastomotic leakage compared with parenteral nutrition. On the eighth postoperative day, the EN group had higher levels of albumin and prealbumin compared with the PN group, suggesting that postoperative EN support is more effective in maintaining patients' nutritional status than PN support. No difference was observed in digestive complications between these two approaches. However, this meta-analysis is characterized by heterogeneity issues, especially regarding the postoperative nutritional status [70]. Furthermore, others suggest that combination of enteral and parenteral feeding is more beneficial, since total parenteral nutrition (TPN) could lead to hyperglycemia in stressed patients. A combination of EN and TPN might have some benefits when compared to TPN alone, such as improvement of intestinal integrity and stimulation of incretin production contributing to improved glucose control in patients undergoing esophagectomy [71]. Moreover, supplemental parenteral nutrition after esophagectomy contributes to better coverage of patients' calorie requirements, since large amounts of enteral nutrition are not usually tolerated in the first postoperative days [72].

The European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines for nutritional support recommend that interruption of nutritional intake is unnecessary after surgery in most patients and in patients who require postoperative artificial nutrition, enteral feeding, or a combination of enteral and supplementary parenteral feeding is the first choice. Also this combination should be considered in patients in whom more than 60% of energy needs cannot be met via the enteral route. Postoperative parenteral nutrition is beneficial in undernourished patients in whom enteral nutrition is not feasible or not tolerated. In addition, postoperative parenteral nutrition is beneficial in patients with postoperative complications impairing gastrointestinal function that are unable to receive and absorb adequate amounts of oral/enteral feeding for at least 7 days [28]. Moreover, the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines for critically ill patients recommends that patients who have undergone major upper gastrointestinal tract surgery and EN is not feasible, PN should be initiated (only if the duration of therapy is anticipated to be more than 7 days). Unless the patient is at high nutrition risk, PN should not be started in the immediate postoperative period, but should be delayed for 5–7 days [73]. In conclusion, although enteral nutrition seems to be a safe and feasible option postoperatively in terms of immunological parameters and postoperative complications, no firm conclusion can be drawn regarding postoperative nutritional markers that reflect patients' nutritional status.

3.2. Time of feeding

3.2.1. Early enteral nutrition

The initiation of enteral feeding after esophagectomy remains a controversial topic and many studies examine whether or not early enteral feeding affects negatively or positively the postoperative outcome. One study that investigated early enteral feeding after esophagectomy included 208 patients who received enteral nutrition postoperatively and were divided into three groups (Group 1, 2, and 3) based on whether they received EN within 48 h, 48–72 h or more than 72 h, respectively. The postoperative complications, length of hospital (LOH) stay, days for first fecal passage, cost of hospitalization, and the difference in serum albumin values pre- and postoperatively were all recorded. Group 1 had the lowest thoracic drainage volume, the earliest first fecal passage, and the lowest LOH and hospitalization expenses of all the three groups. The incidence of pneumonia was higher in Group 3. Finally, all postoperative outcomes of nutritional status were worst in Group 3 [74]. Similarly, one systematic review demonstrated that early oral EN was associated with reduced length of stay and did not increase complication rates [75]. More randomized clinical trials are required to confirm the results from retrospective studies that indicated that early EN promotes early recovery of intestinal movement and better recovery from systemic inflammation [66]. In addition, current literature is inconclusive with respect to the right time of EN administration postoperatively, that is, EN initiation within 24 h versus EN initiation during 24–72 h [76, 77].

3.2.2. Enhanced recovery after surgery (ERAS)

Early enteral nutrition is an essential part of fast-track surgery protocols in order to maximize the effects of enhanced recovery. Fast-track programs incorporate new methods regarding anesthesia, nutritional care, pain control, and surgical techniques in the preoperative, intraoperative, and postoperative period, aiming to promote postoperative rehabilitation of patients [78]. ESPEN guidelines recommend that all cancer patients undergoing either curative or palliative surgery should be managed within an enhanced recovery program postoperatively; within this program every patient should be screened for malnutrition and if deemed at risk, given additional nutritional support [79]. Nutritional aspects of ERAS could be summarized as follows: limitation of preoperative fasting, preoperative fluid and carbohydrate loading, and initiation of oral diet on the first postoperative day [80]. A recently published review demonstrated that utilization of enhanced recovery programs in esophageal cancer patients was associated with a reduction in the incidence of anastomotic leak, pulmonary complications, and length of hospital stay, but no significant change was observed in postoperative mortality or readmission rate. Nevertheless, there was significant heterogeneity between the studies in terms of enhanced recovery protocols, surgical approach, and utilization of neoadjuvant therapies that should be taken into account [81]. Results from a randomized controlled clinical study showed that the implementation of a fast-track protocol improved postoperative clinical recovery and cellular and humoral immunity of patients undergoing esophagectomy for esophageal cancer (**Table 2**) [82]. In this context, the implementation of fast-track programs in esophagectomy patients is promising, but the majority of patients included in the studies are relatively healthy patients. More randomized controlled studies and evidence-based research are required in order to justify the routine use of fast-track protocols in esophageal cancer patients [83].

3.3. Perioperative immunonutrition

Immunonutrition is one of the most debated topics in nutritional support of esophageal cancer patients. The term immunonutrition includes formulas that contain immune-modulating substances, such as arginine, glutamine, ribose nucleic acid, and omega-3-fatty acids. A recent review concluded that postoperative enteral immunonutrition could be promising in improving humoral immunity in patients undergoing esophagogastric resection, but this improvement is not related to a reduced hospital stay, nor does it reduce the rate of infections. The authors reported that there is heterogeneity regarding the types of operations undertaken (two studies included patients undergoing esophagectomy, three studied patients undergoing gastrectomy,

Day	FTS pathway
POD1	Jejunostomy tube feeding 500 ml (starting at 20 ml/h)
	Early postoperative mobilization program
	(>2 h out of bed)
	Physical therapy and nebulizers
	Remove urine catheter
	Head of bed put at 30°
	Supply albumin
	Chest tube to suction
	Promoted to lung recruitment
POD2	Jejunostomy tube feeding 1000 ml (40 ml/h)
	Chest tube to suction
	Expand mobilization (>4 h out of bed)
	Continue physical therapy and nebulizers
	Continue supply albumin
POD3	Jejunostomy tube feeding 1500 ml (60–80 ml/h)
	Remove chest tube
	Remove epidural catheter
	Expand mobilization (>6 h out of bed)
	Continue physical therapy and nebulizers
	Continue supply albumin
POD4	Gastrograffin opacification of upper gastrointestine
	If swallow shows no leak, advance patient to oral drink
	Jejunostomy tube feeding 1500 ml (60–80 ml/h)
	Continue physical therapy and nebulizers
	Education on aspiration precaution
	Education on chewing and swallowing
POD5	Jejunostomy tube feeding 1500 ml (60–80 ml/h)
	Advance patient to a full liquid diet
	Continue aspiration precautions
	Continue physical therapy and nebulizers
POD6	Increase liquid diet
	Decrease jejunostomy tube feeding
	(500 or 1000 ml)
	Continue aspiration precautions
	Continue physical therapy and nebulizers
POD7	Remove jejunostomy tube
	Full liquid diet
	Discharge home on soft diet and liquid diet
	Continue aspiration precautions

Note: FTS: Fast track surgery. Adapted from Chen et al. [82].

Table 2. Daily guideline of postoperative care of patients with fast-track surgery pathway.

and one had patients undergoing both operations). Additionally, the included randomized clinical trials used different formulations of enteral immunonutrition and standard enteral nutrition, further limiting the accuracy of the results. Moreover, not all studies reported the same outcomes as far as inflammatory and immunological markers are concerned. Therefore, the authors suggest that there is no convincing evidence in terms of routine immunonutrition in patients undergoing esophageal resection for cancer [84].

On the other hand, preoperative nutritional supplementation with immune-enhancing formulas was associated with reduced infectious complications, duration of hospitalization, improved short-term survival and less mortality in patients with esophageal cancer. These results highlight the possible need to provide immunonutrients before surgery to obtain sufficient levels at the time of surgical stress when there is an increased need for stimulation of the immune system [85]. One meta-analysis that included studies with patients that underwent esophagectomy, gastrectomy and pancreatectomy, demonstrated that patients who received immunonutrition postoperatively, had a significantly lower risk of wound infection and shorter length of hospital stay. No significant effect of immunonutrition on other postoperative morbidities and mortality was noticed [86]. The reduction in hospital stay and/or in postoperative complications seems to compensate for the higher cost of immunonutrition compared to standard enteral feeding in a cost-effectiveness analysis [87]. According to ESPEN guidelines on nutrition in cancer patients, upper gastrointestinal tract cancer patients undergoing surgical resection should receive oral/enteral immunonutrition in the context of traditional perioperative care [79]. Furthermore, ASPEN guidelines suggest the routine use of an immunemodulating formula (containing both arginine and fish oils) in the surgical intensive care unit for the postoperative patient who requires enteral nutrition therapy [73].

Synbiotics, which are a combination of prebiotics and probiotics, are speculated to have beneficial effects on human health, but little is known about their clinical value in patients who have undergone esophagectomy. Administration of synbiotics prevented postoperative deterioration of the intestinal microfloral environment and suppressed excessive inflammatory response, possibly by exerting immunomodulatory effects and by inhibiting bacterial translocation [88, 89]. Additionally, synbiotics led to decreased incidence of severe diarrhea and lower interruption or reduction of enteral nutrition. Passage of flatus postoperatively occurred significantly earlier in patients who received synbiotics than in the control group, suggesting that synbiotics maintain intestinal motility [88]. Taking all the aforementioned things into consideration, larger scale studies are needed in order to define whether or not immunonutrition has beneficial effects on the postoperative outcome of esophageal cancer patients. Future research should focus on the optimal dose of specific immunonutrients, on the timing (preoperatively and/or postoperatively) and duration of immunonutrition delivery and clarify which is the target group the intervention should be addressed to.

3.4. Type of feeding

Enteral feeding postoperatively seems to be the method of choice for uncomplicated esophageal cancer patients. Enteral feeding options after surgery include mainly nasoenteric tubes and jejunostomy catheters, in order to bypass recently constructed anastomoses. However there is no general agreement regarding the best method for postoperative feeding, and the optimal access route remains questionable. Tube-related complications include occlusion, catheter displacement and local cellulitis at the site of insertion. More severe complications include leakage into the peritoneal cavity resulting in peritonitis, volvulus at the point of fixation to the anterior abdominal wall, aspiration pneumonia, necrotizing fasciitis or jejunal necrosis at the site of catheter insertion and septicemia [90, 91].

A retrospective analysis of 90 patients who underwent esophagectomy demonstrated that early enteral nutrition can be administered using three different routes (nasojejunal tube, jejunostomy tube, and pharyngostomy tube) with similar results regarding tube-related complications, length of stay, and 30-day morbidity [92]. Another study of esophageal cancer patients with dysphagia examined the effects of jejunostomy feeding on weight loss and treatment outcomes. The palliative group of patients was able to maintain a stable weight despite the presence of cancer cachexia. This was also evident in the esophagectomy group of patients despite the catabolic effect of the operation, indicating the effectiveness of the jejunostomy feeding catheter as a means of nutritional support. The feeding catheter was well tolerated by the majority of patients (86.8%) and the most frequently occurred complications included catheter clogging (10.1% of the study population) and catheter dislodgement (3.1% of the study population) [93]. A randomized clinical study that compared nasoenteric tubes to jejunostomy feeding in upper gastrointestinal tract cancer patients showed that the length of enteral feeding use was less in the nasoenteric group and parenteral feeding was required more frequently than in jejunostomy feeding group. Complications related to the different feeding routes were similar between the two groups [94]. A recent review investigated the best route for enteral nutrition following esophagectomy (oral intake, jejunostomy, or nasojejunal tube feeding) in terms of postoperative complication rates, percentage of patients meeting their nutritional needs, weight loss, tube feeding complications, mortality, patient satisfaction, and length of hospital stay. Complications and catheter efficacy did not differ between postoperative nasojejunal tube feeding and jejunostomy tube feeding. Moreover, jejunostomy feeding patients were able to meet their short-term nutritional requirements, but data concerning long-term outcomes and patients satisfaction were scarce. This review concluded that the best route for the delivery of early enteral nutrition postoperatively is still unclear [75].

ESPEN guidelines on enteral nutrition in surgical patients recommends that tube feeding should be applied in patients who cannot start early oral nutrition, including those undergoing gastrointestinal surgery for cancer and patients with obvious undernutrition at the time of surgery, in whom oral intake will be inadequate (<60%) for more than 10 days. Initiation of tube feeding should start within 24 h after surgery with a low flow rate (i.e. 10–20 ml/h) due to limited intestinal tolerance. Placement of a needle catheter jejunostomy or nasojejunal tube is recommended for all candidates for tube feeding undergoing major abdominal surgery. When anastomoses of the proximal gastrointestinal tract have been performed, enteral nutrition should be delivered via a tube placed distally to the anastomosis [95].

Postoperative nutritional management of esophageal cancer patients can be summarized as in **Figure 2**.

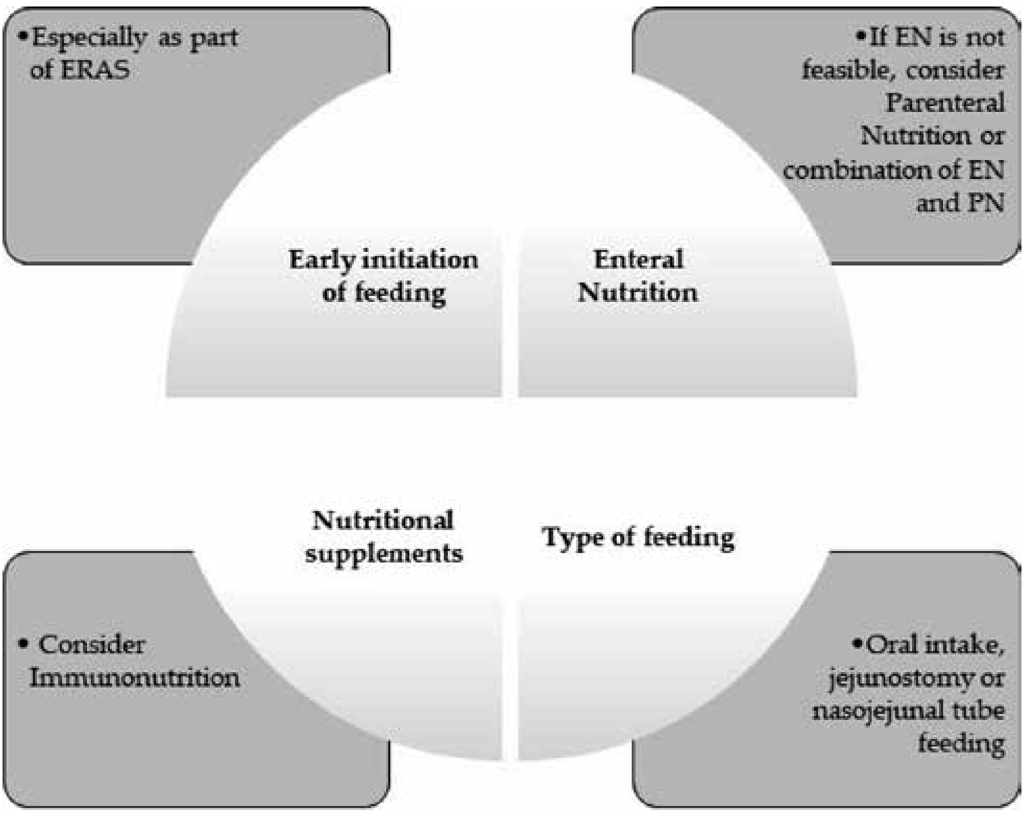

Figure 2. Postoperative nutritional management of esophageal cancer patients.

4. Nutritional care during chemoradiotherapy

4.1. Nutrition issues during chemotherapy and radiotherapy

Currently, perioperative chemotherapy is frequently administered for the treatment of resectable advanced esophageal cancer. The neoadjuvant administration of chemotherapy or chemoradiotherapy preoperatively results in reduced tumor size before surgery. Perioperative chemotherapy improves significantly disease-free survival and overall survival rates compared to surgery alone. However, a great percentage of these patients are not able to complete the planned postoperative chemotherapeutic regimens. This is mainly caused because of postoperative complications and impaired nutritional and physical status [96–98]. Gastrointestinal disorders caused by chemotherapy itself, including nausea, vomiting, diarrhea, and anorexia, negatively affect patients' quality of life and make completion of chemotherapy difficult. Neoadjuvant chemotherapy induces changes in body composition which, in turn have negative impact on clinical outcomes. Results from a small cohort of esophageal cancer patients showed that 26% of patients were sarcopenic before the initiation of neoadjuvant chemotherapy and this percentage increased to 43% after its completion. There was a significant loss of fat mass and skeletal muscle mass which was associated with risk of circumferential resection margin positivity [50]. In another study, sarcopenia was present in 56 and 67% of patients before and after neoadjuvant chemoradiotherapy, respectively. This decrease in muscle mass was predictive of postoperative mortality in the stage III–IV subgroup of patients [99]. Furthermore, most of the radiotherapy-related toxicities are strongly associated with patient's nutritional status. Esophagitis is the main toxicity during radiotherapy in esophageal cancer patients. These patients often suffer from pain and difficulties in swallowing [100]. One study in patients receiving concurrent chemoradiotherapy revealed that malnutrition was observed in 83.8% of patients, while 68.8% of patients developed severe dysphagia. Malnourished patients developed more treatment-related toxicities compared to those without malnutrition. Patients with impaired nutritional status presented severe dysphagia, anorexia, severe nausea/vomiting, and severe hematologic toxicities more frequently than those in a good nutrition status [17]. Although nutritionally related side effects occur frequently, nutritional assessment of patients with cancer receiving chemoradiotherapy is often omitted in the clinical setting. Scientific research has to focus on nutritional interventions during neoadjuvant chemoradiotherapy or postoperative adjuvant therapy that seems to improve patients' nutritional status, alleviate symptoms and increase tolerance to therapies.

4.2. Nutritional interventions during chemoradiotherapy

The type and timing of nutritional interventions during chemoradiotherapy challenge the caregivers, since a multidisciplinary approach seems more effective in managing treatment's side effects. Current literature emphasizes mainly on the immunomodulatory effects of some nutrients, on the impact of oral/tube administration of high-energy, and/or high protein supplements on the clinical outcome and on patients education about selecting an enriched diet. In cancer patients, it has been shown that the use of supplemental formulas and *n*-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can improve body composition, preserve muscle mass, and possibly reverse or stop the development of cancer cachexia [101]. A controlled, randomized prospective, double-blind, multicenter study investigated the impact of enteral nutrition (via percutaneous endoscopic gastrostomy (PEG)) enriched with EPA and DHA on body composition, nutritional and functional status of esophageal and head and neck cancer patients undergoing concurrent chemoradiotherapy. There was a tendency toward improvement regarding loss of body cell mass and body weight following chemoradiotherapy, but did not reach statistical significance. However, Karnofsky score and subjective parameters, such as the NRS 2002 and the SGA score were significantly improved in the experimental group compared with the control group, indicating improved nutritional and functional status [102]. Similar results reported by another randomized double-blind clinical trial showed that administration of immunonutrition during chemoradiotherapy in head and neck and esophageal cancer patients was advantageous over standard enteral nutrition in terms of body weight, lean body mass, serum albumin levels, NRI assessment, plasma antioxidant capacity, and functional capacity [103].

Moreover, immunonutrition can modulate the immunological and inflammatory systems, thus reducing the risks of concurrent chemoradiotherapy. One randomized clinical trial examined the effects of immunonutrition on serum cytokine and inflammatory markers, and cellular immunity in locally advanced esophageal cancer patients undergoing chemoradiotherapy. The levels of C-Reactive Protein (CRP) and TNF increased more during treatment in the control group (standard enteral nutrition) than in the treatment group, whereas all other markers did not differ significantly between the two groups [104]. In addition, the impact of immunonutrients on immune system of head and neck and esophageal cancer patients during chemoradiotherapy was examined in another randomized clinical trial. Immune cells metabolism and functions were assessed at the initiation and at the completion of treatment. The experimental group had better adaptation to the systematic inflammation and oxidative stress, as indicated by $CD4^{+}/CD8^{+}$ T-lymphocyte counts ratio, CD3 membrane expression, polymorphonuclear cells CD62L and CD15 densities, reactive oxygen species (ROS) production, and peripheral blood mononuclear cells production of pro-inflammatory prostaglandin-E2 [105].

Another role of immunonutrition is the potential protection against chemotherapy-induced toxicities. Miyata et al. compared the effects between enteral nutrition rich in *n*-3 fatty acids (900 mg/d) and enteral nutrition poor in *n*-3 fatty acids (250 mg/d) on chemotherapy-related adverse events and inflammatory markers during neoadjuvant chemotherapy in esophageal cancer patients. This randomized control trial showed no significant difference in the incidence of grade 3/4 leukopenia and neutropenia, but stomatitis was observed less frequently in the *n*-3-rich group, than in the *n*-3-poor group. Grade 3/4 diarrhea was also observed less frequently in the *n*-3-rich group than in the *n*-3-poor group, but this was not statistically significant. Moreover, *n*-3-rich enteral nutrition seems to have hepatoprotective properties by preventing an increase of aspartate aminotransferase and alanine aminotransferase values [106].

Synbiotics seem also to mitigate chemotherapy-related side effects through adjustments to the intestinal microbiota. A randomized clinical trial investigated the effects of synbiotics in esophageal cancer patients undergoing neoadjuvant chemotherapy, on the intestinal microbiota, and the adverse events of treatment. Severe lymphopenia and diarrhea were less frequent in patients who received synbiotics than in the control group. Furthermore, febrile neutropenia occurred less in the synbiotics group compared to the control group [107]. Chemotherapy may disturb the intestinal microbiota, leading to reduced production of organic acids in the bowel, impaired mucosal integrity, and increased harmful bacteria. These, in turn, may induce chemotherapy-related toxicities, such as diarrhea and infectious complications [108]. Administration of synbiotics results in increased concentrations of short-chain fatty acids, such as acetate and propionate. These fatty acids are an important energy source of enterocytes, maintain intestinal environment acidity and intestinal motility. Synbiotics also maintain the number of beneficial bacteria and inhibit the overgrowth of possible diarrheal pathogens, thus reducing the incidence of diarrhea [109].

ESPEN guidelines on nutrition in cancer patients recommend the supplementation with long-chain *n*-3 fatty acids or fish oil to stabilize or improve appetite, food intake, lean body mass, and body weight in patients with advanced cancer undergoing chemotherapy and at risk of weight loss or malnourished [79]. It is therefore evident that immunonutrition enhances immune system and exerts anti-inflammatory properties, but the promising effects on clinical outcome during chemoradiotherapy in esophageal cancer are still under investigation. Additional clinical trials are needed to determine the preferred type, timing and duration of immunonutrition required to reduce inflammation and chemotherapy-induced toxicities, and maintain muscle mass.

Nutritional interventions, other than that examining the impact of specific immunonutrients on chemoradiotherapy-related outcomes, include nutritional counseling and/or enteral supplements in order to maintain stable body weight and cope with feeding difficulties (**Table 3**). A recent randomized controlled trial compared the effects of a walk-and-eat intervention versus conventional medical care for patients with esophageal cancer undergoing neoadjuvant chemoradiotherapy. This intervention consisted of a structured walking protocol and weekly nutritional advice including weight and intake evaluation, counseling to overcome feeding difficulties, supplementation, if necessary, with enteral formulas, and patient's education concerning food texture modification and oral care before and after eating. During chemoradiotherapy, the group that received the walk-and-eat intervention had 100-m less decline than controls in walk distance, 3 kg less decrease in handgrip strength, and 2.7 kg less reduction in body weight. Moreover, the experimental group had significantly reduced rates of intravenous nutritional support and wheel chair use [110]. Another randomized trial tested the effects of an interdisciplinary nutrition support team on clinical and hospitalized outcomes of esophageal cancer patients receiving concurrent chemoradiotherapy. Nutritional support included dietary counseling, oral nutritional supplements, enteral nutrition, and parenteral nutrition according to patient's needs. At the completion of treatment, nutritional status of patients in the interventional group was better compared to control group, as demonstrated by prealbumin, transferrin, and albumin levels. Bone marrow suppression and complications related to infections were significantly lower in the nutritional support group. Nutritional intervention was also associated with a lower average length of hospital stay and in-patient cost [111]. Furthermore, nutritional intervention improved survival of esophageal cancer patients treated with definitive chemoradiotherapy. It is noticeable that this effect was observed only if nutritional support was provided at baseline (dietary advice, oral supplementation, or major intervention), and not if provided later in the treatment course [10].

According to ESPEN, in patients receiving radiotherapy, especially radiotherapy of the head and neck, thorax, and gastrointestinal tract, an adequate nutritional intake should be ensured primarily by individualized nutritional counseling and/or with use of oral nutritional

Nutritional counseling
Oral supplementation
Immunonutrition
Synbiotics
Parenteral nutrition support

Table 3. Nutritional interventions during chemoradiotherapy.

supplements, in order to avoid nutritional deterioration, maintain intake, and avoid radiotherapy interruptions. In addition, for patients undergoing curative anticancer drug treatment who cannot meet their nutritional requirements despite counseling and oral nutritional supplements, ESPEN recommends supplemental enteral nutrition or, if this is not sufficient or possible, parenteral nutrition [79]. Therefore, assessment and maintenance of good nutritional status at baseline may be a simple and cost-effective intervention that improves clinical outcomes in esophageal cancer patients during chemoradiotherapy treatment.

4.3. Stent insertion

There are various types of stents available, such as self-expandable metallic stents, self-expandable plastic stents, and biodegradable stents. Esophageal stenting can be implemented to relieve dysphagia during preoperative chemotherapy and/or radiotherapy. A systematic review investigated the impact of stent insertion during neoadjuvant treatment on dysphagia improvement. Placement of an esophageal stent significantly improved overall dysphagia scores in all 12 studies reviewed. However, no consistent improvement in nutritional status was observed, defined by body weight and albumin levels. Moreover, stent insertion was associated with complications, such as migration and chest pain, frequently resulting in stent removal or replacement [112]. The European Society of Gastrointestinal Endoscopy (ESGE) does not recommend self-expandable metal stents placement as a bridge to surgery or prior to preoperative chemoradiotherapy, since it is associated with a high incidence of adverse events. Other options, such as feeding tube placement are preferable and should be considered in dysphagic or malnourished patients in the neoadjuvant setting [113].

5. Palliative care

Management of patients undergoing noncurative treatments due to advanced disease is difficult, since the goals are not to cure patients but to improve length and quality of remaining life. Nutritional support is a crucial part in the palliative care as long as its benefits outweigh its costs. Patients with metastatic disease present for the clinician not only clinical but ethical issues as well. Dysphagia is the main symptom in patients with unresectable disease which aggravates malnutrition and requires nutritional intervention [114]. Nutritional support of these patients includes intravenous fluids for hydration, feeding tubes, parenteral nutrition, and stent placement in order to supplement dietary and caloric intake. Various techniques have been proposed to manage dysphagia, such as brachytherapy, self-expanding metal stents, thermal laser therapy, and photodynamic therapy. Each one of them has specific advantages and risks that should be taken into consideration. The authors of a recent meta-analysis of 53 randomized controlled trials concluded that self-expanding metal stent insertion is safe, effective, and improves dysphagia faster compared to other modalities. High-dose intraluminal brachytherapy is a satisfactory alternative and might provide additional survival benefit with a better quality of life. Combinations of brachytherapy with self-expanding metal stent insertion or radiotherapy seem to be the preferable option addressed to inoperative patients [115]. ESGE recommends placement of partially or fully covered self-expandable metal stents for palliative treatment of malignant dysphagia over laser therapy, photodynamic therapy, and esophageal bypass [113].

Moreover, in esophageal cancer patients with short life expectancy unsuitable for esophageal stenting, percutaneous endoscopic gastrostomy (PEG) may be a suitable means in order to achieve nutritional support, while allowing patients to be at home [116]. Endoscopically assisted nasogastric tube feeding is also a feasible palliative option for nutritional support, with a low complication rate. Tube-feeding patients had significantly higher enteral calorie intake, higher serum albumin, shorter hospital stay, and longer median survival compared to those who received *nil per os*, according to a retrospective study of patients with malignant esophageal obstruction [117]. Palliative care in the terminal phase should be followed in an individualized manner. ESPEN recommends that in dying patients, artificial hydration and nutrition are unlikely to benefit patients. Nevertheless, in acute confusional states, patients might receive a short and limited hydration to rule out dehydration as precipitating cause [79].

6. Conclusion

Esophageal cancer patients suffer from malnutrition and cannot easily meet their nutritional needs. Nutritional assessment, in the perioperative phase, but also in patients undergoing chemoradiotherapy should be performed regularly, in order to identify undernourished patients. Regarding the perioperative management of these patients, early enteral nutrition support seems to be the method of choice in uncomplicated patients, especially as a part of ERAS programs. However, the impact of immunonutrition on clinical outcome is still under investigation. During chemoradiotherapy, prevention of weight loss is of great significance and might be achieved through close nutritional monitoring. Nutritional support mainly encompasses dietary counseling, oral supplementation, tube feeding, and combination of them and has promising results in ameliorating nutritional status and affecting the oncologic outcome. Moreover, patients with terminal-stage esophageal cancer might benefit from early stent insertion in order to reduce dysphagia. Individualized nutritional support should be addressed to every patient who is in need of nutritional intervention.

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Section 3

Other Disorders of the Esophagus

Congenital Diseases of Esophagus

Mehrdad Hosseinpour and Bahareh Ahmadi

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69577

Abstract

Esophageal atresia (EA) presents some of the greatest technical hurdles that pediatric has to face. Postnatally, the classical clinical presentation of an infant with EA is an abnormally mucousy infant who is drooling excessive amount of saliva. Diagnosis confirmed when an orogastric tube cannot be passed through the mouth into the stomach. Examination should assess the as cardiac, anal limb. The purpose of the surgery is to divide the trachea esophageal fistula (TEF) and to restore esophageal continuity blind-ending upper esophageal. Achalasia is an uncommon disorder of esophagus dysmotility. Patients typically present with a history of progressively worsening dysphagia that begins with solid foods. The initial diagnosis test in child with dysphasia is usually a contrast esophagogram. Classic findings include a dilated, dysmotile esophagus and a bird's beak deformity at the gastroesophageal junction. The main treatments of achalasia are esophageal myotomy, balloon dilation or botulism toxin. Esophageal diverticula are often first suspected on Chest X ray(CXR) due to presenting symptoms. These lesions can cause wheezing, dyspnea, hemoptysis and recurrent pneumonia due to airway compression and dysphasia due to esophagus compression. These duplications should be further investigated by CT scan or Magnetic resonance imaging (MRI). The preferred method of treatment is thoracoscopy or thoracotomy.

Keywords: esophageal atresia, esophageal diverticula, achalasia

1. Esophageal atresia

1.1. Embryology

Esophageal atresia (EA) and trachea esophageal fistula (TEF) are important human birth defects of unknown etiology and represent a challenge to the pediatric surgeons. The great majority of cases of EA and TEF occur as sporadic events. However, there is emerging evidence of an important role for genetic factors.

Embryologically, the respiratory system is derived from the foregut endoderm with the appearance of the laryngo tracheal groove in the ventral floor of the foregut, just caudal to the level of the pharynx [1].

In broad terms, there have been two contrasting theories to explain how the respiratory foregut separates from the gastrointestinal foregut.

In first theory, the respiratory system develops as a result of rapid outgrowth from the original foregut tube [2], but in an alternative theory, there is active growth of a mesenchymal septum which develops in the coronal plane and, as a result, separates the foregut lumen into ventral (respiratory) and dorsal (gastrointestinal) structures [3]; however, direct evidence of septum formation has been lacking, casting doubt on this theory.

The separate process occurs in human embryo between 28 and 37 days of postfertilization. A number of theories have been put forward for disturbed TE malformation, which themselves reflect the theories of normal development.

In first theory, the normal development of trachea is the result of rapid longitudinal growth of the tracheal primordium away from the foregut, and TE malformation is caused by a failure of tracheal growth, the result of which is a compensatory overgrowth of the undivided foregut with the bronchopulmonary buds originating directly from the foregut [4].

In second theory, failure of separate process of ventral trachea and dorsal esophagus is the main case of TE malformations [5].

Interestingly, EA is not a part of this initial malformation. Atretic proximal esophagus is a result of late rearrangement of the cranial foregut, resulting in a blind-ending structure.

Finally, genetic models show that the expression of some factors is fundamental for separation of anterior foregut and loss of this dorsoventral boundary expression domains disrupts the physical separation of the foregut [3].

1.2. History and classification

The first survivors of EA and TEF were not recorded until 1939 with Leven and Ladd achieving success with staged esophageal repair. Cameron Haight is fully credited with the first successful primary repair and survival of a 12-day-old female neonate [6].

In 1929, Vogt proposed the first anatomical classification of EA and TEF, based on radiological and postmortem findings. **Figure 1** and **Table 1** show a working classification based on the frequency of each anomaly (gross classification).

1.3. Associated anomalies

EA can be divided clinically into isolated EA and syndromic EA, occurring at the same rate. The most frequent associated malformations encountered in syndromic EA are [7]:

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Cardiac (20–30%)

Vertebra (10–15%)

Limb (5–19%)

Anorectal (15–25%)

Renal (5–14%)

Nonrandom association has been documented as well. Two of these are the VACTERL (**V**ertebral, **A**norectal, **C**ardiac, **T**racheo-**E**sophageal, **R**enal and **L**imb abnormalities) and CHARGE association (**C**oloboma, **H**eart defects, **A**tresia of choan, developmental **R**etardation, **G**enital hypoplasia and **E**ar deformities).

1.4. Clinical presentation

A newborn with EA is often noted to have difficulty clearing saliva. Episodes of coughing, choking and even transient cyanosis may be observed.

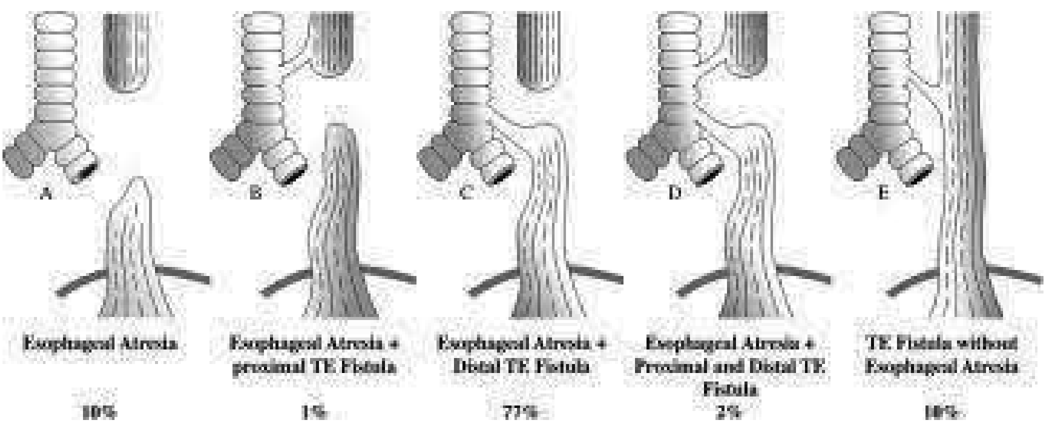

Figure 1. Schematic presentations of EA and TEF.

Type C	**85%**	**EA and distal TEF**
Type A	7%	Isolated EA
Type E	4%	TEF without EA
Type D	3%	EA and proximal and distal fistula
Type B	1%	EA proximal fistula

Table 1. Gross classification of EA and TEF.

1.5. Diagnosis

1.5.1. Antenatal

1. Polyhydramnios
2. Absence of stomach bubble in sonography

1.5.2. Postnatal

The diagnosis of EA and TEF is confirmed by the failure of passage of a firm nasogastric tube. Coiling of the tube can be demonstrated in plain chest and abdominal X-ray (**Figure 2**). Presence of gas-filled intestine loops below the diaphragm is a landmark of associated TEF. In isolated EA, a featureless gasless abdominal X-ray is observed.

1.6. Preoperative preparation

After a complete physical examination, routine blood work including cross match should be performed.

Other evaluations are included as:

1. Preoperative echocardiogram (to assess for major structural abnormalities, the position of aortic arch)
2. VACTERL workup
3. Genetic consultation

1.7. Operative technique

Extrapleural approach through the right fourth intercostal space allows the identification of azygos vein, TEF and upper pouch. Division of TEF and primary anastomosis of the esophagus are essential elements of operative technique. TEF is identified along the vagus nerve. TEF is encircled by tape and divided nearly trachea and closed. One-layer stitch anastomosis is the most standard procedure for end-to-end anastomosis [8].

1.8. Postoperative care

The infant should be nursed in the intensive care unit following repair of EA and TEF. Intravenous fluids and broad spectrum antibiotics are continued. Weaning from ventilation need not to be unduly prolonged in the stable infants with satisfactory anastomosis. In most cases, transanastomotic tube feeding can be commenced after 48 h and slowly increased as tolerated by the infant.

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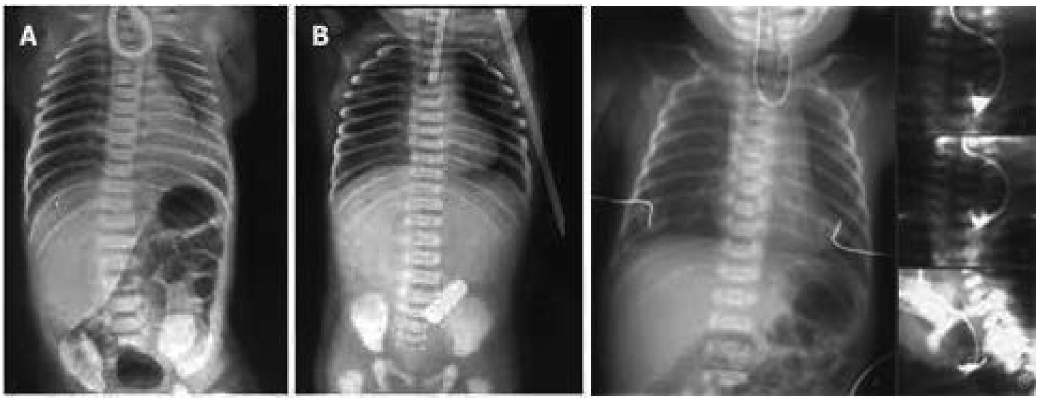

Figure 2. Example of a CXR demonstrating EA.

2. Achalasia

2.1. Embryology

Achalasia is an uncommon disorder of esophageal dysmotility, with an annual incidence of only one in 100,000 individuals.

Achalasia is derived from Greek word, meaning 'no relaxation' of the lower esophageal sphincter (LES). It is suggested that the cause of achalasia is ischemia following excessive rotation of the gut as a volvulus in utero in the embryo which selectively destroys ganglion cells [9]. Other tissues recover but neurons do not regenerate, leaving denervated gut forever.

In normal swallowing, coordinate peristaltic contractions of the esophageal body and transient relaxation of the LES cause the antegrade propulsion of ingested foods.

In patients with achalasia, this normal relaxation fails to occur. Patients with achalasia often have a reduced number of ganglion cells, and the ganglion cells are surrounded by an inflammatory infiltrate. It seems that the primary pathology must be in the wall of the gut and not in the CNS. This ganglion cell loss is best seen in Auerbach's plexus between the esophageal muscle layers.

In second theory, an autoimmune mechanism, which is the progressive partial destruction of the ganglion cells and the inhibitory neurons that normally mediate LES relaxation, is the main cause of Achalasia.

2.2. History

Achalasia/cardiospasm was first described by Sir Thomas Wills in 1672. In 1881, Von Mikulicz described the disease as a functional problem, but Heller (1913) was the first surgeon to perform esophagomyotomy successfully [10].

2.3. Associated anomalies

Achalasia in children has been associated with trisomy 21, triple-A syndrome (achalasia, alacrima and AcTH insensitivity) and familial dysautonomia, but most are sporadic.

2.4. Clinical presentation

In pediatric practice, most achalasia is reported during adolescence, more often in boys. Typical symptoms include dysphagia, vomiting or regurgitation of food, chest pain and weight loss or failure to thrive. Adolescents with achalasia usually suffer from halitosis. In children, respiratory symptoms consistent with aspiration may occur.

Bronchiectasis has also been reported due to recurrent aspiration specially in Down`s syndrome cases.

2.5. Diagnosis

2.5.1. Contrast study

The initial test in the child with dysphagia is usually contrast esophagogram in supine and upright positions. Classic findings include a dilated esophagus and a 'bird beak' deformity at the gastro-intestinal junction (GEJ) (**Figure 3**). In long standing disease, the progressively redundant esophagus can adopted a sigmoid shape.

2.5.2. Manometry

The standard test for achalasia remains manometry. Pressure recording shows absent or diminished peristalsis in the upper esophagus, elevated LES pressures, and minimal or absent LES relaxation.

2.5.3. Endoscopy

Endoscopy may demonstrate pooling of retained fluid within the esophagus and stasis-induced inflammation. Although mild resistance is encountered in endoscopy, but it can be passed in to the stomach, ruling out of mechanical stricture.

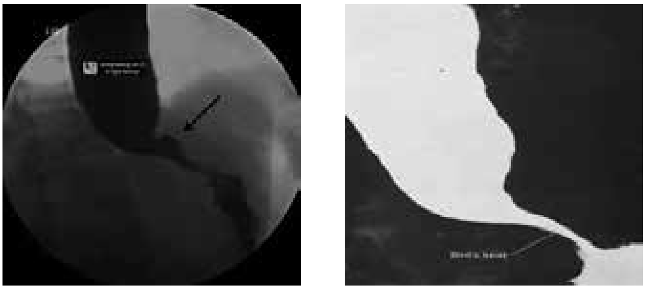

Figure 3. Esophagram demonstrating the 'bird's beak' deformity of achalasia.

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2.6. Nonoperative management

2.6.1. Balloon dilation

Balloon dilation of the LES is the most common nonoperative management in achalasia in children; however, symptomatic relief is transient, and thus, repeated dilations are required.

2.6.2. Intrasphincteric toxin injection

Botulinum toxin injection lowers Les pressure by inhibiting acetylcholine release from nerve endings. This effect is also transient, requiring repeated injection [11].

2.7. Operative technique (modified Heller's cardiomyotomy)

Cardiomyotomy for achalasia requires division of the lower esophageal sphincter. This can be accomplished with a thoracic or abdominal approach, open or minimally invasively, with or without a concomitant antireflux procedure [12, 13].

3. Esophageal diverticulum

Esophageal diverticulum is a sac or pouch that protrudes from the esophageal wall, and it is rare in children. It is thought to be caused by an increase in the intraesophageal pressure associated with either distal esophageal motility disorders or periesophageal inflammation [14].

Esophageal diverticulum characterized according to their pathogenesis as either traction or pulsion. Traction diverticulums are true that occur in the mid esophagus secondary to inflammation process in the mediastinum causing an external force on the esophagus.

Pulsion diverticula is a pseudodiverticulum. There are two types of pulsion diverticula: Zenker diverticula and epiphrenic diverticula. Epiphrenic diverticulas occur with increased pressure against the upper and lower esophagus sphincters.

Zenker diverticulum (ZD) is a false diverticulum of the posterior esophagus between the cricopharyng and inferior constrictor. This area of anatomical weakness is known as Killian`s triangle. ZD occurs with high intraluminal pressure created during swallowing [15]. ZD is more likely to occur with increased size of Killian`s triangle [16]. Majority of these cases involve anatomical esophageal deformities or iatrogenic injury in the early postnatal period [17].

Esophageal diverticulum is classified into three categories according to the site of development: pharyngoesophageal diverticulaes, bifurcation diverticulaes and epiphrenic ones [18].

Pediatric esophageal diverticulums were classified according to their physiology by Meadows in 1970 [16]. He described nine types of diverticula in children and infants: cricopharyngeal diverticulum, pulsion diverticulum (Zenker types), duplication of esophagus (epiphrenic and nonepiphrenic), traction diverticulum from the middle third of the esophagus, diverticulum arising in scar tissue, false diverticulum above a congenital stenosis, and traumatic pseudodiverticulum after trachea esophageal fistula repair. Only nonepiphrenic duplication, traumatic, pulsion and congenital diverticula may involve the pharyngoesophageal junction.

Duplication of the esophagus results from a defect in tabulation of esophagus in division of the embryonic foregut [19]. These duplication cysts consist of double layers of smooth muscle that are covered with epithelium. Two-third of them are located in lower third and one-third in the upper/middle third of esophagus [20]. Mostly, they do not communicate with esophagus wall but the duplication cysts as a separate malformation locate along or in continuity with native esophagus [21].

Esophageal duplication cysts can be associated with other congenital anomalies such as small intestinal duplication, esophageal atresia, trachea esophageal fistula, and spinal abnormalities including scoliosis, hemivertebra and fusion [19, 22].

Traumatic pharyngeal pseudodiverticulum is caused in neonates by traumatic catheterization through the esophagus causing perforation of the pharynx and incorrect insertion of a nasogastric tube [23, 24].

Congenital pharyngoesophageal diverticulum is a true diverticulum that contains all normal esophageal musculomucosal layers. Few cases are reported that allow no valid conclusions as to their etiology [25].

Pulsion diverticulum is rare in children, and the reported cases were 6-month- to 10-year-old children. Some related mechanisms include incoordination between movement of food out of the mouth and relaxation of the cricopharyngeal, motility disorder and developmental muscle weakness [16, 26, 27]. No clinical or radiological differences exist between pharyngoesophageal diverticulum and pulsion diverticulum; both are posterior diverticulum that only distinguished by histological exams [28].

Chronic impaction of the foreign body has been proposed as the activating factor of pharyngoesophageal diverticula [27]. Foreign body ingestion is frequent in children, especially between 6 months and 3 years of age [29]. Majority of them travel the gastrointestinal tract without any adverse effects [30]. The cricopharyngeal sphincter is a well-known area of upper digestive tract, narrowing where foreign bodies are likely to get blocked. It is hypothesized that chronic impaction of the foreign body at the level of the cricopharyngeal muscle-induced muscle hypertonia responsible for the development of the pouch [28].

3.1. History

(1) Gastrointestinal symptoms: gagging, dysphagia, odynophagia, vomiting, regurgitation, dysphagia, failure to thrive, anorexia, epigastric pain, gastrointestinal hemorrhage, halitosis and poor feeding [31, 32].

(2) Respiratory symptoms: choking, cyanosis [17], dyspnea, wheeze, cough, stridor, respiratory distress [31], recurrent bronchiolitis, pneumonia and aspiration [32].

3.2. Diagnosis

- Barium swallow
- CT scan
- Esophageal endoscopy

3.3. Treatment

The management of esophageal diverticula includes both conservative and surgical treatments. If the child is asymptomatic, conservative treatment and careful follow-up are recommended. However, when the patient has complications related to esophageal diverticula, then surgical treatment is considered [33].

The traditional surgical treatment for esophageal diverticula is either a diverticulectomy or a diverticolopexy. However, in recent years, minimally invasive surgery such as thoracoscopic or laparoscopic treatment has become popular.

Recently, flexible endoscopy using CO_2 laser technique has been developed for the treatment of esophageal diverticula [34].

3.4. Postoperative care

Most of patients show no symptoms and are discharged from the hospital. In some center, esophageal endoscopy is done after months, later to show existence of narrowing or residual diverticulum in esophagus.

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Prescription of Proton Pump Inhibitors in Elderly Subjects in Real Life: A Retrospective Study in a Gastroenterology Department

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.70526

Abstract

The proton-pump inhibitor (PPI) is an effective and widely used treatment but may cause side effects, especially for the elderly. Materials and methods: this is a cross-sectional study including 45 patients older than 65 years, followed at our outpatient and treated with PPIs for at least a year. The indication for PPI, the results of any endoscopy, and the quality of the tolerance of these molecules is specified by the data folder. During the consultation, we conducted an interrogation to an update of the history and medications to our patients and a type checking of the molecule, the dose, and the quality of the observance. Results: patients were divided into 32 women and 13 men with a mean age of 75 ± 7 years (65–92). The average length of PPI use was 6 ± 4 years (1–16) with a consumption of a double dose for at least 1 year in 28.8% of cases. The prescribed dose was higher than the recommended dose in at least 15.5% of cases. PPIs were well tolerated. One patient had presented a microscopic colitis, revealed by diarrhea regressed after discontinuation of PPIs. Conclusion: PPIs were prescribed in elderly subjects by gastroenterologists, in a university center, with a high dose and long. In our series, this treatment is well tolerated in the elderly.

Keywords: aged person, drug interactions, drug-related side effects, drug utilization, proton pump inhibitors

1. Introduction

Proton pump inhibitors (PPI) constitute a very effective and used treatment at present [1–3]. Previously, they would seem to cause undesirable effects and medicinal interactions probably serious and badly known, especially for the elderly person often fragile and exposed to a polypharmacy [4]. On the other hand, it is a very expensive therapeutic class and frequently used in an inappropriate way [2–4]. In Tunisia, the use of these medicines to the old subject, in the public structures, by specialists, was not studied. So, we have led this study to realize an evaluation of the professional practices concerning the prescription of these molecules, by gastroenterologists, in a teaching hospital (CHU) of the Tunisian South, to the geriatric population.

The objectives of our study were:

1. Specify the main indications and the modalities of the long-term prescription of the PPI to the old subjects and compare them with the international recommendations.
2. Evaluate the observance, the tolerance, and the possible medicinal interactions of the prescribed PPI in the long term to the elderly subjects.
3. Specify, through our results and review of the literature, the difficulties were met and the risks incurred during the prescription of these medicines to the elderly and proposed strategies to overcome them in our current practice.

2. Material and methods

It was about a retrospective study including 45 subjects of more than 65 years old followed in the external consultation of the gastroenterology department of Hédi Chaker hospital of Sfax, having consulting between July 01st, 2015 and December 31st, 2015. The PPI indication, the results of a possible initial endoscopic exploration, and their tolerance were specified by the data of the file. During the consultation, we realized an interrogation with the aim of checking the molecule's type, the dose, and the quality of the PPI observance. The criteria of inclusion were as follows: an upper age or equal to 65-year-old during the beginning of PPI treatment and PPI consumption at least three times a week during a duration of more than 12 months. The criteria of noninclusion were represented by the absence of an exhaustive list of the personal histories of patients and their medicines. The evaluation of the best use of the PPI was realized by referring to the current recommendations of the High Authority of Health and the French Agency of sanitary safety of the products of health (Afssaps) in 2007 [5]. The data were analyzed by using the statistical software SPSS 20.0.

3. Results

The average age of our patients was of ±75 7 years (65–92). About 1/3 of the patients were less than 70 years old (**Figure 1**). In our study, a clear feminine predominance was noted with a sex ratio H/F of 0.4 (**Figure 2**). The majority of our patients were of urban origin (60%) (**Figure 3**). The distribution of the patients according to antecedent is specified as in **Table 1**. Excepting the

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pathology that justifies the PPI use, 25 patients (55.4%) had at least 3 medical antecedent with a daily average number of medicine consumption of 4.8 ± 4.3 (0–17). Six patients had osteoporosis, diagnosed before the establishment of the PPI in a case and after the establishment of the PPI in the five remaining cases. The average deadline separating the beginning of taking the PPI and the discovery of the osteoporosis was of 2.5 years (1–4). No control of the bone densitometry was asked during the follow-up of our patients who have a normal initial examination. Two patients (4.4%), with antecedent of ischemic heart disorder with angioplasty, were treated by clopidogrel (Plavix®) neither with any precaution's closed view to the type of the molecule nor with the schedule of taking PPI. During our interview, we recommended them to keep an interval of 12 hours between the consumption of the PPI and that of the clopidogrel. The main indication of the PPI at our patients was the gastroesophageal reflux (GER) (75.6%) (**Figure 4**). Before the prescription of the PPI, 41 patients (91%) underwent upper digestive endoscopy FOGD. The results of this examination were dominated by the association of a peptic esophagitis and a hiatal hernia (**Table 2**). Among the four remaining patients:

- The FOGD was refused by two patients having abdominal pain
- The FOGD was made after a deadline of using of the PPI (2 years and 6 months respectively) in two patients having typical clinical signs of GER.

Five patients having a normal FOGD had:

- Typical symptoms of GER in three cases
- Abdominal pain in a case
- A long-term treatment by nonsteroidal anti-inflammatory drug (NSAID) in a case.

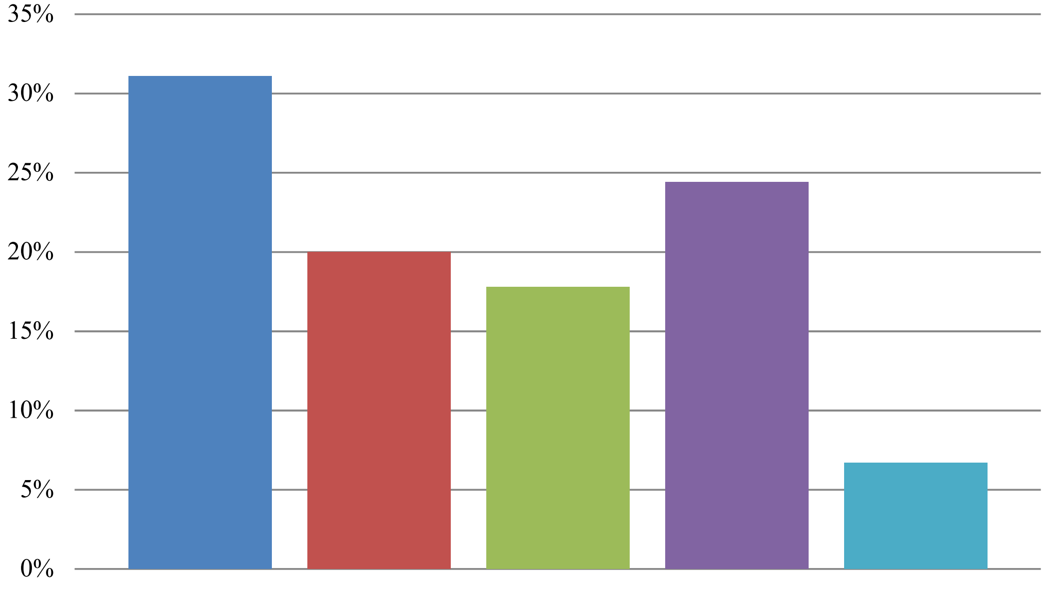

Figure 1. Dividing patients according to the age.

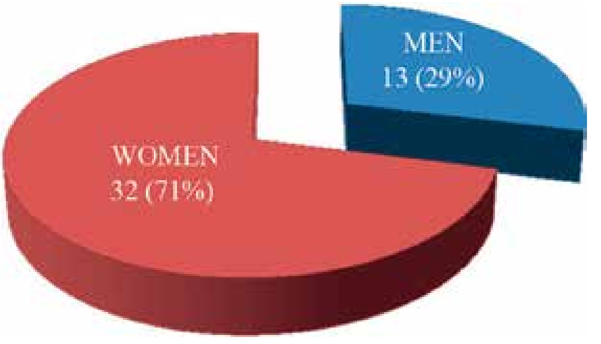

Figure 2. Dividing patients according to sex.

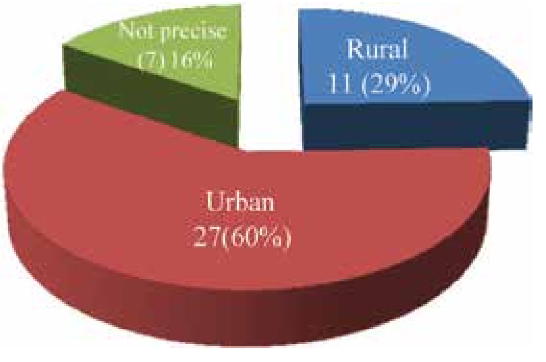

Figure 3. Dividing patients according to their geographic origin.

Antecedents	N (%)
HTA	24 (53.3)
Rheumatologic pathology	16 (35.6)
Dyslipidemia	11 (24.4)
Heart disease	9 (20)
Diabetes	8 (17.7)
Osteoporosis	6 (13.3)
Anemia	2 (4.4)

Table 1. Dividing patients according to antecedents.

The FOGD data at five patients who had abdominal pain motivating the endoscopy were the following ones:

- A bulbar ulcer in one patient
- Bulbar ulcerations in one patient

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- Ulcerated antral gastropathy associated with a bulbar ulcer in one patient
- A congestive gastropathy in one patient
- Normal FOGD in one patient

Gastric biopsies were realized in all the patients who had a bulbar ulcer or bulbar ulcerations. These biopsies were concluded with the absence of the helicobacter pylori in all cases. It was probably caused by the intermittent consumption of AINS in these patients. During the follow-up, only three patients had undergone an endoscopic control, having two peptic stenosis and one Barrett esophagus (BO). It revealed the disappearance of the stenosis in both patients and the absence of dysplasia in the third.

During the period of study (in July 01st, 2015–December 31st, 2015), the PPI availability in the pharmacy of the hospital and in the health centers was omeprazole in the form of 20 mg capsules. Concerning the years preceding the study's period, the molecules availability in the hospital list were either the omeprazole in the form of tablets or 20 mg capsules, or the lansoprazole in the form of 30 mg capsules.

However, these medicines were not always available in this pharmacy and\or in the pharmacies of health centers (frequent breaks of the stock). As a result, some patients would have used other molecules, which they had bought from nearby pharmacies. The interrogation of the patients and their parents was not able to specify the type of these molecules. The average duration of the PPI treatment was of 6 ± 4 years (1–16) with a duration of more than 2 years in 34 cases (75.6%). The PPI was prescribed at the rate of a simple daily dose for 29 patients (64.4%) and of a double daily dose for 5 patients (11.1%). For the rest of the patients, the treatment was prescribed:

- At first, in simple daily dose, during an average duration of 39.1 months (2–96) and then in double daily dose for 9 patients (20%) during an average duration of 4.5 years (1–10).
- At first in double daily dose and then in simple daily dose for two patients (4.4%). The duration of taking the simple dose was of 2 months for a patient and 9 months for the second and that of the double dose was of 6 years and 18 months respectively.

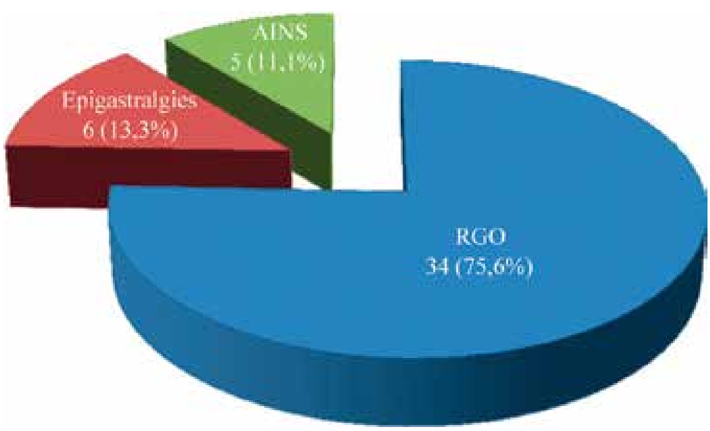

Figure 4. Dividing patients according to PPI indications.

Localization and types of lesions	N (%)
Isolated esophageal lesions	8 (19.5)
Peptic esophagitis OP	4
Peptic stenosis	2
Mycosic esophagitis	1
Barrett esophagus	1
HH/G isolated	1 (2.4)
OP + HH	10 (24.4)
Isolated gastric lesions:	7 (17.1)
Congestive antral gastropathy	3
Ulcerated antral gastropathy	2
Nodular antral gastropathy	1
Pyloric big folds	1
Isolated duodenal infringement:	2 (4.9)
UB	1
Bulbar ulcerations	1
Multiple locations of the lesions:	8 (19.5)
HH + congestive antral gastropathy + bulbar ulcer	1
OP + HH+ bulbar ulcerations	2
OP + HH+ congestive antral gastropathy	1
OP + bulbar ulcerations	1
Ulcerated antral gastropathy + UB	2
HH + bulbar ulcerations	1
FOGD normal	5 (12.2)
Total	41 (100)

OP: peptic esophagitis; HH: hiatal hernia.

Table 2. Dividing patients according to the data of initial FOGD.

The change of the PPI dose was indicated by the evolution of the symptoms motivating their prescription. So, the increase in doses was secondary in the persistence of the symptoms in spite of a good observance of a simple dose, whereas the decrease in doses was motivated by the decrease in the frequency of the symptoms under a double dose of treatment.

The characteristics of seven patients treated straightaway by an PPI double dose are detailed in **Table 3**. The recommendations of the HAS were not respected within the frameworks of:

- The indication of the FOGD in four cases (9%): because of the absence of realizing an FOGD before prescribing the PPI for four patients having abdominal pain or symptoms of GER with an age > 60 years.
- The PPI indication in two other cases (4.4%): having a prescription of the PPI in front of abdominal pain with a normal FOGD, for one case and a congestive gastropathy in another case, without prescribing long-term AINS in two cases. These two situations do not establish an indication for a treatment by a PPI according to the HAS recommendations.
- the PPI posology:
  - Seven cases (15.5%) were treated straightaway by an PPI double dose. Indeed, according to the HAS recommendations, the interest of a double dose was not even demonstrated in RGO case with a severe esophagitis (except in not healing case and subject to a good observance of the treatment, where an increase in the posology can be proposed). So, no indication, among those of our patients, justifies an IPP treatment with one double dose straightaway. For the other cases, it was difficult to judge the concordance of posology with the recommendations against the difficulties of specifying the molecule's type of the prescribed IPP (omeprazole or lansoprazole), because the recommended posology, within the framework of our study's indications, is the full dose (or simple dose) for the omeprazole and the half-dose for the other molecules. The average duration of using PPI with our patients was of 6 ± 4 years (1–16). During the follow-up of our patients, the evaluation of PPI tolerance and the efficiency of the PPI, realized every 6 months, were based on anamneses data without any complementary examination. Furthermore, updating the antecedent list and the patients' treatments was not realized in a systematic way at every consultation. Among our patients, 31 (75.6%) had a good observance for the PPI. The nonavailability of the PPI in the public sanitary structures was the cause of the limited observance.

No.	Age (years)	Sex	Indication of the IPP	Duration of the DD of the PPI (months)	Endoscopic data
1	72	F	Abdominal pain	12	Congestive antral gastropathy
2	84	M	+ NSAID GER	2	Ulcerated antral gastropathy
3	76	F	Abdominal pain	9	+ bulbar ulcer
4	78	F	GER	60	Congestive antral gastropathy
5	82	M	GER	48	HH/G, OP type 2
6	78	F	GER	24	Peptic stenosis
7	68	M	GER	12	Normal

HH: hiatal hernia, GER: gastroesophageal reflux, NSAID: regular consumption of non steroidal anti inflammatory drugs OP type 2: peptic esophagitis type 2.

Table 3. Characteristics of patients treated by double dose (DD) of PPI.

The PPI did not cause any symptoms in 44 patients (97.7%). The remaining patients were presented after the consumption of lansoprazole double dose during 1 year (in front of a refractory GER) with profuse diarrhea. The colonoscopy revealed a normal colonic mucous membrane, but the colonic biopsies had revealed a microscopic colitis of colitis collagen type. Stopping the use of PPI has entrained the disappearance of the diarrhea. Because of the absence of treating the GER by famotidine in the dose of 40 mg/d, the patient was treated by the omeprazole in the dose of 20 mg/d). A few days after the beginning of the treatment, the evolution was marked by the reappearance of the diarrhea. So, the PPI was stopped. For the GER treatment, the patient was treated by a double dose of famotidine associated with the sodium alginate with a satisfying control of symptoms without diarrhea.

4. Discussion

The PPI are an expensive medicinal class and widely prescribed in the world. Indeed, they represented more than 16 million of prescriptions in France in 2008 and about 101 million prescriptions in the United States in 2006 [5, 7]. A recent study, led in Denmark, has revealed a greater increase in the prescription of the PPI during the last decade [8]. In Tunisia, the PPI prescription was not evaluated on the national scale, but the development of several generic medicines since 2013 (10 for omeprazole, 6 for esomeprazole, 4 for lansoprazole, and 1 for pantoprazole) suggests an increasing in the prescription during these last years [9].

The overuse of the PPI is a notorious problem in the world. Numerous studies were interested in the evaluation of the good use of this therapeutic class by basing itself on the recommendations. In the United States, in 2007, a study showed that 54% of the prescriptions of IPP were not adapted [10]. In France, a report from the accounts commission of the Social Security in October, 2009 reported that 15% of the IPP would prescribe out the planned indications. According to this report, 65% of the IPP prescriptions for GER in 2008 were concerned with patients more than 65 years old [11]. Furthermore, in retirement homes, this medicinal class was prescribed for the old subjects in 21.8–37.8% of cases according to the studies [3, 12] However, few studies were interested in the harmlessness of the PPI in the long term, and particularly to the elderly [13].

In spite of its retrospective and monocentric character, with a limited number of patients and impossibility to study the effect of every PPI molecule alone, this study has allowed us to evaluate, for the first time in Tunisia, the tolerance of these medicines, in short and medium terms, as well as the current modalities of their prescription, to old subjects, by gastroenterologists, in a Tunisian CHU.

In our study, the PPI indications were not in agreement with the recommendations in 4.4% of the cases. This percentage was lower than that found in a study led in an American urban geriatric university health center, which was 29% [2]. This fact could be related to the more limited number of patients in our study (45 vs. 100 in the American study) and to the use of different recommendations concerning the good use of the PPI.

Concerning the PPI dose prescribed in our study, it was higher than the dose recommended in at least 15.5% of the cases. This fact could be partially explained by the unavailability, in our public sanitary structures, of some PPI molecule dosages (such as tablets or capsules of lansoprazole of 15 mg), which could impose to the prescriber an increase in doses, because of the economic problems of patients who cannot get themselves treated on their own responsibility in the private pharmacies. However, the increase in the PPI doses was found in a prospective French study evaluating the practices in general medicine to the patients of 75 years old and more, where the full dose represented 53% of the prescriptions in prevention of the gastroduodenal lesions or for the EGR without esophagitis, whereas the recommended dose, in these indications, was half of the dose [14].

In our study, the duration of the prescribed PPI was more than 2 years in 34 cases (75.6%). This result was found in another study where two-third of the old subjects was treated by PPI during more than 2 years [14]. However, the indications of the extended treatment by IPP are limited in the symptomatic periods of EGR or in case of treatment by long-term AINS after 65 years, or in case of a bulbar ulcer Hp (−). This prolonged duration was related to a strong adherence of the patients who felt a bounce effect of the symptoms while stopping the PPI and insisting by consequence on extending the prescription in near the prescribers.

According to our study, the PPI was tolerated well, during an average follow-up of 6 years, with a single unwanted effect (2.3%), a type of diarrhea was related to a microscopic colitis. The well-tolerated character of PPI with long term, to the elderly, was found in other studies [15]. In a study, a type of case witness, by comparing old subjects treated by PPI versus others without PPI, the diarrhea was independently related to the PPI use with an odds ratio of 1.60 [1.20–2.15] [12]. The PPI incrimination in the induction of microscopic colitis is also well documented in the literature with an odds ratio of 6.4 for the collagenous colitis [16]. Other potential unwanted effects of the PPI were described in the literature, in particularly the elderly, such as:

- The consequences of the malabsorption: hyponatremia [17, 18], deficiency in vitamin B12 [19] and hypomagnesemia [20, 21] (which could have serious consequences such as confusion [22, 23])
- The infections, particularly, the bacterial pneumopathies [24] and the intestinal infections, especially to *Clostridium difficilae* [25]
- Osteoporotic fractures [26, 27]
- On the other hand, medicines decreasing the acid gastric secretion such as the long-term PPI would be theoretically capable of leading the genesis of gastric tumors, and even colorectal; in fact, the hypergastrinemia is led by these treatments [28, 29].

In our study, six patients (13.3%) had an osteoporosis without arisen pathological fracture during the follow-up. The PPI incrimination in the genesis of this disease cannot be realized in this study, caused by the absence of a comparison with a witness group, especially that the osteoporosis is frequent in the Tunisian old subject with 23.4% prevalence in Tunisian woman aged more than 50 years old [30]. No control of the densitometry bone and no supplementation by the association vitamin D + calcium were realized during the follow-up of our patients. This decision could be explained by the controversial character of the results of the studies. Indeed, several observational studies and meta-analyses evaluated the PPI effect, alone or in association with biphosphonates, concerning the risk of fractures. In these studies, the PPI use was associated with a higher risk of pathological fractures (particularly of the hip and the vertebras) favored by an osteoporosis, but the association strength was low most of the time. The PPI impact would be higher in case of a good adhesion to high daily doses [31]. In fact, the role of the multiple confusing factors (represented by the age, the female, body mass indexes, the alcoholism, the smoking, the antecedent of falls or previous fractures, the neurological and hematological diseases and the use of antidepression, anxiolytics, antipsychotics, antiepileptics, diuretics, and antidiabetics) could explain the weak character of this association. Moreover, Kaye et al. showed the absence of PPI association at a higher risk of pathological fractures, to a population of 1098 patients having no risk factor of osteoporosis [32]. Also, the supervision results in the long-term tolerance of treated patients by PPI, within the framework of two clinical trials (followed forward looking until 12 years), and hazardous pathological fractures [33] did not appear. Finally, only 1–5% of fractures on osteoprotic bone would be attributed for the PPI use [31].

So, in the United States, the administration of food and medicine (FDA) considered the low clinical impact, neither justifying a calcium supplementation nor a regular supervision of the osseous density [34]. The mechanisms at the origin of changing of the osseous density by PPI are represented by the decrease in the ionization and the absorption of the calcium and the inhibition of the osteoclastic activity, compulsory for the norm progress of the physiological osseous reshaping [13]. Concerning hypomagnesemia risk, no patient in our study benefited from a magnesium plasmatic dosage. This attitude is debated in the literature, due to the absence of a forward-looking study with a long-term follow-up. However, in 2012, after a literature review, Hess et al. recommended a dosage of magnesemia plasmatic rate before the introduction of an PPI long-term treatment, particularly with the patients treated with other hypomagnesemiants medicine (such as the digoxine, the diuretics), with a regular follow-up. In case of discovering a hypomagnesemia, these authors recommended a stop of PPI with an addition of calcium and magnesium [35]. In this case, according to these authors, the substitution of the PPI by the anti- histaminic receptor (anti-H2), which does not lead to a hypomagnesemia risk, could not be recommended. If the symptoms related to the hypersecretion acid were not controlled by the anti-H2, occasional cures by PPI can be prescribed by a biological supervision [35]. In front of the potentially serious complications of the hypomagnesemie, especially with elderly (vomiting, diarrhea, hypokalemia, hypocalcemia, muscular tetanizes, rhythm disorders, the extension of the interval QT, the convulsions, the confusion) and through the frequent undesirable effects, which is considered rare if the PPI was prescribed by recommended doses, the FDA recommended a magnesemia dosage before the introduction of a PPI treatment:

- If the treatment duration would be extended.
- Or in case of association with other hypomagnesemiants medicine.

A regular supervision of the magnesemia was also recommended by the FDA in the quoted situations, without specifying the monitoring methods [34]. In a recent literature review, besides the authors had recommended this conduct to the elderly or those having chronic diseases (diabetics, kidney insufficiency, or having a cardiovascular pathology) [31].

No patient of our series presented an intestinal or lung infection during the follow-up, but the retrospective character of our study does not eliminate this fact, because the patients could forget or neglect to mention these infections to the consultant physician of the IPP, during the various consultations. The PPI was different in the increase of infectious risk that caused the decrease in the gastric acidity, which is considered as an antimicrobial natural barrier. A meta-analysis demonstrated the PPI association with an increasing risk of Salmonella infection, Campylobacter, and other bacteria except *Clostridium difficilae* (CD) (odds ratio = 3.33 [1.84–6.02]) [36].

The increasing risk of the infection by the CD was demonstrated by three meta-analyses published in 2012 (odds ratio between 1.48 and 2.31) [37–39] with an increase of this risk in case of IPP association with an antibiotic treatment [37]. However, the other confusing factors such as the elderly and the comorbidity were not specified in most of these studies [31]. On the other hand, a recent retrospective study recommended avoiding the PPI use with the patients having antecedent of repeated infections with CD [40].

Because of these data, the FDA recommended considering the infection diagnosis with CD in case of persistent diarrhea under PPI and limiting the use of these molecules to the effective minimal dose during the shortest possible duration, to avoid this risk [41]. The upper age to 65 years constitutes an individual factor risk for the infections with CD [42]. Furthermore, the consequences of this infection (diarrhea, colitis, megacolon, colonic perforation) are more serious in the elderly. Moreover, in England and in WALES, the death rate related to these infections is concerned mainly with elderly more than 65 years old [43]. So, this risk justifies the limitation of the IPP prescription, particularly to the elderly.

Concerning the pneumonia's risk under PPI, the pathophysiological mechanisms of this association were not clearly established, but they are essentially represented by the gastric bacterial colonization, the change of the bacterial oropharyngeal flora, and the lung microinhalation of these bacteria [31]. The results of the case-witness studies and meta-analysis suggest a moderate increase in the arising out of community-acquired pneumonia by using the PPI [31]. The odds ratio found in a recent literature review was 1.49 (1.16–1.92) [44]. The community-acquired pneumonia risk by using the PPI is related to the treatment duration with a more important risk after a month of starting the treatment (odds ratio = 2.1 (1, 39–3, 16)) independently of the posology and of the patient's age [31]. Though there is the absence of forward-looking studies and the intervention possibility of confusing factors, these data suggest the importance to limit the IPP prescriptions to the validated indications.

In conclusion, the responsibility of the PPI in the happening of events, which is unwanted and sometimes serious, was demonstrated, but the studies were often retrospective and sometimes biased and the strength of the association was low most of the time with an odds ratio 2 [31]. However, you should not consider these medicines as simple "gastric defenders" without any risk and to limit their prescription to the validated indications, to the recommended posology, during a well-determined duration, especially to the fragile elderly subject treated by a lot of drugs.

The PPI use may increase the risk of medicinal interactions (by modifying the absorption of medicine by acting on the gastric pH or by competition on the cytochrome P450 (CYP)) being able to make tilt the balance profit/risk negatively, at the elderly person. Indeed, by increasing the gastric pH, the PPI decreases the dissolution and the solubilization of some administered medicines per bone, such as antifungals (for example, the itraconazole [45]) or the immunosuppressors (such as the mycophenolate mofetil [46]). On the contrary, they can increase the reduction of some medicines such as the saquinavir [47]. On the other hand, the taking of a PPI could theoretically improve the bioavailability of medicines for which an important part of the ingested dose is normally hydrolyzed in acid area (such as penicillin) [48]. Finally, it was demonstrated that the omeprazole increased the bioavailability of the digoxine [49] and the nifedipine [50] by inhibiting at the intestinal level of the isoenzyme 3A4 of the CYP450 and the glycoprotein P.

On the other hand, all the PPIs, except the rabeprazole, are mainly metabolized by isoenzymes 2C19 and 3A4 of the CYP, [51]. At the same time, the PPI inhibit these enzymes. The omeprazole is also a moderate inductor of the CYP 1A2 [52]. Thus, pharmacokinetics interaction risk exists with medicines that are major substrata of these isoforms. The particular case of the interaction between the IPP and the clopidogrel, a platelet antiaggregant in which the efficiency depends on its bioactivation by the CYP 2C19, was widely studied, without formal proof of its clinical impact. The clopidogrel belongs to the class of thienopyridines. It is a prodrug, absorbed by the intestine and then transformed into an active metabolite by the liver via two successive reactions of oxidation by cytochromes P450, and more exact isoforms CYP2C19, CYP3A4/5, CYP2C9, and CYP2B6. By inhibiting the CYP 2C19, the PPI (except for a very weak action for the pantoprazole) decreases the clopidogrel activation and thus its efficiency, hence exposing the patients to ischemic accidents. Numerous retrospective studies confirmed this interaction [53]. According to the FDA's to the healthcare professionals of November 17th, 2009, the association of the omeprazole with the clopidogrel is not advisable. The FDA, presented the pantoprazole as a possible alternative in case of necessary association of an IPP with clopidogrel, because of its slightest inhibitive potential on the CYP 2C19 [54]. As far as the inhibition of the CYP 2C19 by the PPI is reversible and considering the short half-life of the PPI, some authors suggested minimizing the clinical consequences of this interaction by prescribing the PPI in the morning and the clopidogrel in the evening with an interval of 12 hours by separating both the takings [55]. However, the published randomized forward-looking studies did not find this interaction and confirmed the beneficial effects of the PPI on the digestive bleedings [31, 56, 57, 58]. In 2012, these data allowed Afssaps (become ANSM: National agency of Safety of the Medicine) to remove, the PPI-clopidogrel interaction from the thesaurus of the medicinal interactions [59].

However, the ANSM has issued a reserve in its recommendations of 2012 advising to avoid the clopidogrel-omeprazole and clopidogrel-esomeprazole associations [60]. In our series, two patients were treated with the clopidogrel in association with the PPI and they did not receive any information concerning the possibility of a medicinal interaction. Though a formal proof of the clinical impact of this association was absent, we preferred to recommend our patients to space out the taking of both medicines for 12 hours, because of the pantoprazole's unavailability in our public pharmacies.

By taking into account the data of our series, which confirms the concomitant use of several medicines by elderly besides the IPP with the possibility of medicinal interactions, it is important to update the medicines' list taken by the patient at every consultation as well as to recommend him stopping the PPI if this treatment is not anymore indicated. Indeed, one of the main obstacles in stopping the PPI is the rebound effect that is generated. It is established from now on that the stop of a treatment by PPI can lead relapses by rebound effect on the gastric acidity. So, since 1996, an increase of 50% of the gastric acid secretion has been highlighted at nine patients for 14 days after the stop of a three-month treatment by omeprazole to the 40 mg/d posology [61]. In 2009, a randomized trial, with double blind versus placebo, realized at 120 asymptomatic healthy volunteers, confirmed the clinical impact of this rebound effect by showing that only after 8 weeks of a treatment with esomeprazole to the 40 mg/d posology, 44% of the exposed subjects presented the symptoms of rebound effect (heartburns, gastroenteritis ebb: esophageal or dyspepsia) against 15% in the witness group [62] These symptoms arose from the second week following the PPI stop, and they were still described till the end of the follow-up period, that is 4 weeks after the stop. Other studies showed that the rebound effect on the acid secretion lasts beyond 8 weeks after the stop [63, 64]. To the naive subjects for the pylori helicobacter, this effect rebound seems to be proportional in the rise of pH during the treatment, while it tends to be masked by the persistent hypochlorhydria observed at the infected patients by the pylori helicobacter [63]. Other multicentral trials, randomized, in double blind showed that less than a third of patients receiving a long-term IPP, succeeded to stop the treatment without an effect on the control of the symptoms and the quality of life, whereas another third passed to a treatment "in the request" [65, 66]. Several pathophysiological hypotheses were envisaged to explain this rebound effect on the acid gastric secretion, such as a hypergastrinemia [61] or a hypertrophy and a hyperplasia of the cells of the gastric wall [63].

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Caustic Ingestion in Children

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.68604

Abstract

Caustic ingestion (CI) is an unfortunate event that occurs in families with a poor prevention culture. Its prevalence is unknown in developing countries; it occurs mainly in children < 5 years and is more common in boys. The chemical caustic agents are alkaline (85%) or acid products stored in food or beverage containers without warning labels and safety caps. The immediate symptoms include salivation, oropharyngeal burns, vomiting and oropharyngeal/retrosternal pain. Upper endoscopy is the first-line tool to identify the type and extension of oesophageal and gastric damage. A barium swallow performed 2–3 weeks after the CI may identify oesophageal stricture. Dysphagia occurs in about one-third of cases. Regarding the nutritional status, children with dysphagia and/or oesophageal strictures may have lower fat reserves or muscle mass than the cases without these complications, meaning impaired nutritional status. All patients should be hospitalized for evaluation and treatment. Hemodynamic stabilization and adequacy of the patient's airway are priorities; vomiting induction and gastric lavage are contraindicated. Methylprednisolone in II-b oesophageal burns for 3 days diminishes the risk of stricture. Selected cases will require oesophageal dilatations, gastrostomy or oesophageal replacement by colon or stomach. There are other promising agents in the management of caustic oesophageal strictures.

Keywords: caustics, oesophageal burns, oesophageal stricture, dysphagia, child malnutrition

1. Introduction

CI in children and adolescents is an unfortunate event that may lead to significant upper gastrointestinal tract damage manifested in the short term as oesophageal burns and in the long term as oesophageal stricture or acquired motility disorders. A high proportion of these patients may evolve to permanent disability associated to feeding difficulties as well as growth and nutritional impairment. The aim of the chapter is to discuss the experience with our CI paediatric patients treated in a paediatric referral hospital in the context of the published data from other authors.

2. Epidemiology

Although is not a public health problem, CI is a significant issue worldwide, particularly in developing countries in which an unsafe environment is a substantial risk factor for child injury [1]. In 1985, Wasserman reported that approximately 5000 children younger than 5 years ingested lye each year in the United States [2]; in 2008, the USA National Poison Data reported over 200,000 exposures to caustic substances [3]. Unfortunately, the true prevalence regarding this health problem is not known in most developing countries and cannot be extrapolated from publications of series of children with CI treated in paediatric hospitals; however, these publications describe demographic, clinical and treatment characteristics of children from low, lower-middle and high-income countries information is scarce specially in lower-middle income countries [1].

Overall, the paediatric population is the most affected; the highest risk age groups are infants and pre-schoolers [4–13]. This may be attributed to the fact that children younger than 6 years are not able to make reasonable decisions about what they should or should not drink in the context of their developmental stage of motor and sensory skills [8]. Regarding gender, the higher frequency trend of CI in males could be attributed to both a gender-related biological and learned gender-role behaviour of boys different from girls in terms of expressing health and disease and their interaction with risk factors [4–7, 13–15]. A recent publication reveals that children with attention deficit/hyperactivity disorder had a higher risk to suffer CI than children without this condition [16].

Reports related to the social, economic, and educational characteristics that may play a role in families of children with CI are scarce [17]. In this context, the authors performed a case-control study in which the aim was to evaluate the association of socio-demographic factors in a group of 94 children and adolescents with CI; the controls were a random sample of children hospitalized or seen as outpatients in the same paediatric referral hospital and period. The sociodemographic variables were studied using a validated questionnaire. CI occurred at home in 63.8% and at a relative's home in 23.4%. Alkaline products were the most frequently ingested (85.1%); containers had no warning labels in 72.3% and no childproof safety caps in 92.6% of the cases. The sociodemographic variables associated with CI included higher family income, mother's lower education, higher proportion of fathers working as independent professionals, extended family, mother's age < 30 years, and mother's working outside home. The fact that both parents work outside the home and that the mother has a low educational level may reflect a lack of awareness and knowledge of the hazards of corrosive substances kept in the house. Family organization classified as extended implies crowded living conditions and enables both parents to work outside home while other family members take care of their children [18]. Other authors have reported that unsafe homes where safety rules regarding caustic substances are lacking have been identified as a substantial risk factor for CI in children [1, 9, 13, 17, 21]. Sarioglu-Buke *et al.* found that children from families where both parents with low educational level and low socioeconomic status had a higher risk for a CI event. Urganci *et al.* found in a series of 1709 cases that 30% of the mothers were illiterate [13]. Contini *et al.* described most CI particularly in developing countries as being due to parent's lack of knowledge of the hazards of corrosive substances kept in the house, especially among illiterate individuals [1]. Risk factors are summarized in **Table 1**.

2.1. Physiopathology

The physical form, concentration, and pH of the corrosive agent play a significant role in the location and type of resultant injuries [2]. Acid substances lead to coagulation necrosis that usually limits acid penetration and results in damage to the epithelium and submucosal layer. Their low viscosity and specific gravity result in rapid transit to the stomach, and gastric injury is more common than oesophageal injury. Their bitter taste and development of pain with ingestion may result in lower volumes of ingestion. The gastric injury may result in gastric outlet obstruction o perforation [19]. The ingestion of alkalis causes liquefaction necrosis with damage of the epithelium and the submucosa layer with deep penetration and may result in perforation [2]. Injury most typically involves the oesophagus, but the gastric injury may also occur.

Haemorrhage, thrombosis and a marked inflammatory response with significant oedema are seen within the first 24 h of injury [19]. The tissue repair phase extends from the end of the first week through the second week after injury and if the insult has been relatively minor, oesophageal function returns gradually. The healing phase begins around the third week when fibroblast proliferation replaces the submucosa and *muscularis mucosae*; at this time, stricture formation begins [2, 19]. Additionally, lower oesophageal sphincter pressure becomes impaired, leading to increased gastroesophageal reflux, which in turn accelerates stricture formation [20].

Age	**Below 6 years old**
Gender	Boys
Alkali or acid caustic substances at home	Improper storage
	Food or drinks storage containers
	Lack of warning labels
	Lack of security caps
Extended families	Both parents working away from home, children cared for other family members and mother with a low education level

Table 1. Risk factors for caustic ingestion in paediatric patients [18, 21].

In most series, the most commonly reported corrosive agents are alkaline products as caustic soda, sodium hypochlorite and household chemicals [13]. It is essential to highlight that most of these products ingested by children were kept in containers that had no warning labels and no childproof safety caps. These key risk factors should be taken care by worldwide governments by means of health education and implementation of legislative and preventive strategies on labeling, formulation, and packaging of corrosive substances [1, 21].

2.2. Clinical manifestations

The ingestion of acid or alkali substances frequently leads to damage to the gastrointestinal tract. The spectrum damage ranges from mild to severe and may affect the mucosa as well as the muscular layer. In a study performed by the authors in a paediatric referral hospital, the aim was to evaluate the association of clinical data with the oesophageal damage of 94 children who suffered CI. The mean age when the CI occurred was 38.4 months (SD 28.7). Thirty-five cases (37.2%) were females. The higher frequency was in infants (40.4%) and pre-schoolers (45.7%). The symptoms recorded were salivation (77.7%), oropharyngeal burns (76.6%), and vomiting (74.5%), oropharyngeal pain (45.7%), and epigastric pain (18.1%). Symptoms of airway involvement included shortness of breath (14.9%) and retrosternal pain (10.6%) [19]; these signs and symptoms are similar to those reported by other authors in paediatric series [3–7, 9, 12, 13, 21].

2.3. Diagnosis

In a number of cases, CI patients may be symptom-free on admission; in spite of this, endoscopy is mandatory as an effective tool to identify both oesophageal and gastric damage [22]. Even more, the presence or absence of symptoms does not predict the injury severity to the gastrointestinal tract, supporting the endoscopic procedure [23, 24]. The degree of the mucosal injury should be determined by a standardized classification; most colleagues use the Zargar's classification: grade 0 = normal; grade I = oedema and erythema; grade II = linear ulcerations and necrotic tissue with whitish plaques; grade II-a = linear ulcerations and necrotic tissue with whitish plaques and deeper and more circumferential; grade III = circumferential injury which may be transmural with mucosal sloughing, multiple deep ulcerations and areas of necrosis (areas of brown-black or greyish discoloration of mucosa were taken as evidence for necrosis); grade III-a = focal necrosis; grade III-b = extensive necrosis; and grade IV = perforation [25]. A study performed in 206 children reported no complications when the endoscope was advanced beyond the first severe burn; this approach could identify additional oesophageal and gastric lesions that could be missed if the endoscopy is discontinued when finding the first circumferential oesophageal burn, as is usually recommended because of perforation risk [23].

In our series, all cases underwent upper endoscopy within 48 h of CI; in 66 of 78 children (84.6%), we identified moderate or severe oesophageal burns, 76.9% had grade II and 7.7% grade III. An endoscopy plus a barium swallow were repeated after 2 or 3 weeks of the CI to assess mucosal healing and to look for strictures; mucosal healing occurred in all cases but 64.5% had oesophageal stricture [21]. Clinical, endoscopic and image data of our cases are summarized in **Table 2**.

http://dx.doi.org/10.5772/intechopen.68604

	Variable	*n*	%
Symptoms and signs	Salivation	73	77.7
	Oropharyngeal burns	72	74.5
	Vomiting	70	70.3
	Oropharyngeal pain	42	45.7
	Epigastric pain	17	18.1
	Shortness of breath	14	14.9
	Retrosternal pain	10	10.6
	Septic schok[a]	4	4.2
	Dysphagia[b]	23	24.5
Endoscopy	II or III degree esophageal burns[c]	79	84
	Esophageal stricture[d]	46	48.9
Barium swallow	Esophageal stricture	46	48.9

[a]Oesophageal perforation.
[b]Weeks/months after the caustic ingestion.
[c]Admission endoscopy.
[d]Endoscopy performed 2–3 weeks after admission.

Table 2. Clinical data in 94 children with caustic ingestion [21, 38].

In 2012, Uygun *et al.* developed a tool for predicting risk of developing an esophageal stricture without endoscopy called the DROOL score based on the severity and duration of initial signs and symptoms (drooling, reluctance to eat, presence of burns in oropharynx, fever, hematemesis, abdominal tenderness, dyspnea, chest pain and leukocytosis). A DROOL score ≤ 4 was a significant predictor of esophageal stricture with 100% sensitivity and 96% specificity; this score needs further investigation and validation [26]. It has been recently published that a CT scan may offer a more detailed evaluation than early endoscopy in assessing the transmural damage of esophageal and gastric walls and the extent of necrosis; a CT grading system has also been proposed to predict esophageal stricture [27]. These important findings deserve to be validated because this could mean a significant change in the diagnostic approach of these patients.

2.4. Complications

Acute complications such as mediastinitis and oesophageal perforation may occur and they may represent life-threating complications; in selected cases, chest and abdominal radiographs are needed to rule out the presence of free air in the mediastinum or peritoneum. Lateral neck radiographs should be obtained in patients with stridor or hoarseness [28].

Long-term complications frequently include oesophageal stricture and dysphagia [4–9, 11, 13, 18]. In our series, oesophageal stricture occurred in 48.9%; II and III-degree burns were associated with oesophageal stricture ($p = 0.004$) and ingestion of alkaline products ($p = 0.027$). The observation that one-half of patients with stricture did not complain of dysphagia and that some patients with dysphagia had no oesophageal strictures, points to the underlying complexity of the functional and anatomical oesophageal damage induced by the chemical agent as well as to the individual variation in visceral sensitivity [29].

Several studies have reported oesophageal dysmotility after a CI; oesophageal manometry has revealed hypoperistalsis, with normal upper and lower oesophageal sphincter [30, 31]. Rana et al. showed that patients with corrosive injury have prolonged oro-cecal transit time using the lactulose hydrogen breath test, even in the absence of gastric symptoms; this transit time was maximally prolonged in patients with lower third oesophageal scars [32]. Gastric emptying time assessed by radionucleotide scintigraphy after a CI was significantly prolonged in patients with oesophageal stricture, even in the absence of gastric symptoms [33]. Another study reported that oesophageal transit time assessed by scintigraphy was prolonged in one-third of patients with corrosive induced oesophageal strictures, despite having achieved adequate oesophageal dilatation; these authors found that the prolongation of oesophageal transit time correlated with the length of the stricture and that the severity of the dysphagia correlated with the prolongation of total oesophageal transit time [34].

CI with stricture has been associated with increased risk of oesophageal carcinoma with an incidence of 1000 times the expected in normal population; this important finding points the need for endoscopic surveillance 15–20 years after the caustic injury [28, 35].

The severity of the oesophageal damage that occurs frequently in children with CI may limit the normal feeding process leading to malnutrition and growth impairment [18, 22, 36]; it is surprising that there is very little published information regarding the nutritional status. In France, Ganga-Zandzou *et al.* found that the nutritional status in 34 children with oesophageal stricture was not affected [37]; whereas, in Egypt, Hamza *et al.* recorded 15% of malnutrition [15]. In another study performed by the authors, the aim was to evaluate the nutritional status and its association with dysphagia and oesophageal stricture in 62 children with CI. Although the proportion of cases with z-scores of height for age and weight for height below −2SD was low, all anthropometric arm indicators (fat and muscle) of the children with dysphagia and oesophageal strictures were located in the negative area of the z-score curve. In all cases, adiposity z-score values were significantly lower in children with dysphagia or strictures when compared with the cases without these complications. Arm muscle area z-scores showed the same trend. We concluded that children with dysphagia and/or oesophageal strictures associated to CI had lower fat stores and muscle mass than the cases without these oesophageal complications, meaning impaired nutritional status [38]. In this context, both growth and nutritional status surveillance as an effective nutritional intervention protocol should be part of the mid- and long-term monitoring of these patients.

2.5. Treatment

All patients who suffered a CI should be hospitalized and evaluated comprehensively. The clinical history must emphasize the type and amount of caustic and if possible get the product package. Hemodynamic stabilization and adequacy of the patient's airway are priorities. The induction of vomiting or gastric lavage is contraindicated following CI because a re-exposure of the oesophageal mucosa to the caustic agent with further injury may occur [35]. An endoscopic evaluation with an adequate paediatric endoscope performed within the first 24–48 h is essential to evaluate the type and extent of injury to the oesophagus and stomach.

The information about the efficacy of proton-pump inhibitors and H2 blockers to minimize the oesophageal injury in subjects whom ingested caustic is scarce. Cakal *et al.* performed an open clinical trial on 13 adult patients who were admitted due to CI and received omeprazole 80 mg in bolus IV, followed by continuous infusion of 8 mg/hour for 72 h. A control endoscopy was performed 72 h after admission, identifying a significant difference regarding endoscopic healing between the before and after omeprazole infusion ($p = 0.004$); however, this study lacks a control group and is not possible to draw definitive conclusions [39].

The use of corticosteroids is controversial; two meta-analyses did not demonstrate benefits of steroid administration in terms of stricture prevention [40, 41]. In a recent study on 83 children with II-b oesophageal burns, one group received methylprednisolone (1 g/1,73 m/day/3 days), ranitidine, ceftriaxone, and total parenteral nutrition; the control group received the same regimen except methylprednisolone. The outcome variable was oesophageal stricture and it was more frequent in the control group ($p = 0.038$). The duration of total parenteral nutrition was shorter in the steroid intervention group compared with the control group ($p = 0.001$). The authors concluded that high doses of methylprednisolone used for the management of grade II-b oesophageal caustic burns may reduce the risk of stricture [40–42].

The use of antibiotics is controversial and should be considered in each particular case according to the clinical situation, laboratory inflammation values, the extent and type of mucosal damage and the concomitant use of steroids. The indications, dosages, duration and type of antibiotics are usually included in the protocols of each hospital serving this type of patients [19].

During the course of treatment, some patients may require oesophageal dilations and gastrostomy either for retrograde oesophageal dilations or trans-gastrostomy feeding. Topical mitomycin C application has been used recently to improve the results of endoscopic dilatation for short oesophageal strictures and is a promising agent in the management of the long-segment caustic oesophageal strictures, although long-term follow-up is needed to prove its efficacy and to evaluate potential long-term side effects [43]. The use of oesophageal stents and balloon dilators are known options for treating strictures [5, 28, 35].

A small number of cases with strictures refractory to dilation may require oesophageal replacement by a colonic graft or stomach's plasty to set up a gastric tube. Ezemba *et al.* reported a retrospective study of 21 patients who underwent substernal isoperistaltic colonic interposition graft for the management of corrosive oesophageal stricture. The long segment strictures and multiple strictures were the main indications for the procedure; the complications included cervical fistulae (19%), reflux neo-esophagitis (14.3%), graft infarction (9.5%); lethality occurred in 9.5%. In the mid term, dysphagia was completely relieved in 84% of the cases, no regurgitation or nocturnal aspiration was reported [44].

Special attention should be placed on growth, nutritional status and the emotional situation of the affected children and their families. A limited oral intake, decrease in growth velocity and low-fat reserves or muscle mass may require special dietary regimens with adequate energy and micronutrient intake by means of blended or polymeric diets. A CI is a traumatic event that may shake families emotionally, and in some cases, they may require emotional support by family therapists.

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Lymphocytic Esophagitis

Dane Christina Daoud and Mickael Bouin

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69445

Abstract

Lymphocytic esophagitis is a new and rare entity, first described in 2006. Histologically, the esophageal mucosa is characterized by a dense peripapillary lymphocytic infiltrate and an intercellular edema without granulocytosis. To this day, it is not yet considered as a disease. Its etiology and clinical significance are still unclear. The predominant symptom is dysphagia and the main endoscopic feature is a normal esophagus. The absence of relationship between lymphocytic esophagitis and specific clinical conditions justifies further studies. Currently, it remains a histologic entity.

Keywords: lymphocyte, esophagitis, dysphagia, Crohn, CD4, CD8, motility

1. Introduction

Lymphocytic esophagitis is a histopathological entity described for the first time in 2006 by Rubio *et al*. [1]. Subsequently, several publications have confirmed the existence of this new condition. Research has allowed us to better characterize the histology of Lymphocytic esophagitis. Unfortunately, clinical presentation and treatment remain poorly understood.

2. Prevalence

Lymphocytic esophagitis is a very rare condition. In 2012, Haque *et al*. estimated its prevalence to 0.1% in the United States [2]. In their cohort that included 129,252 esophageal biopsies, a diagnosis of lymphocytic esophagitis was made in only 119 patients. Since Rubio's first publication, there is a marked increase of its incidence, probably because of pathologists' and gastroenterologists' awareness [3].

Moreover, since it is a novel entity and most of the studies are from North America, worldwide prevalence has not been evaluated.

3. Histology

A small amount of intraepithelial lymphocytes is normally present in the esophagus [4, 5]. A majority of these lymphocytes are CD8 T cells, whereas CD4 are a minority and usually present in the lamina propria. An increase in CD8 T cells is seen in peptic and eosinophilic esophagitis. In addition, this lymphocytosis is generally accompanied by eosinophils and/or neutrophils [5–8].

Compared to other esophageal pathologies, lymphocytic esophagitis is characterized by an isolated lymphocytosis. The main histologic findings are a dense peripapillary intraepithelial lymphocytic infiltrate, an intercellular edema known as spongiosis, as well as the absence or rarity of granulocytes (**Figure 1**) [1]. The intraepithelial lymphocytes express CD3, CD4, and CD8, as shown by immunohistochemistry [1, 9, 11].

Unfortunately, because the histologic criteria are not yet standardized, it can sometimes lead to misdiagnosis. For instance, the presence of rare intraepithelial granulocytes is accepted in lymphocytic esophagitis [1, 2, 10, 11]. However, granulocytes can be found in various esophageal diseases, making diagnosis more difficult [11]. The acceptable number of granulocytes still needs to be better defined.

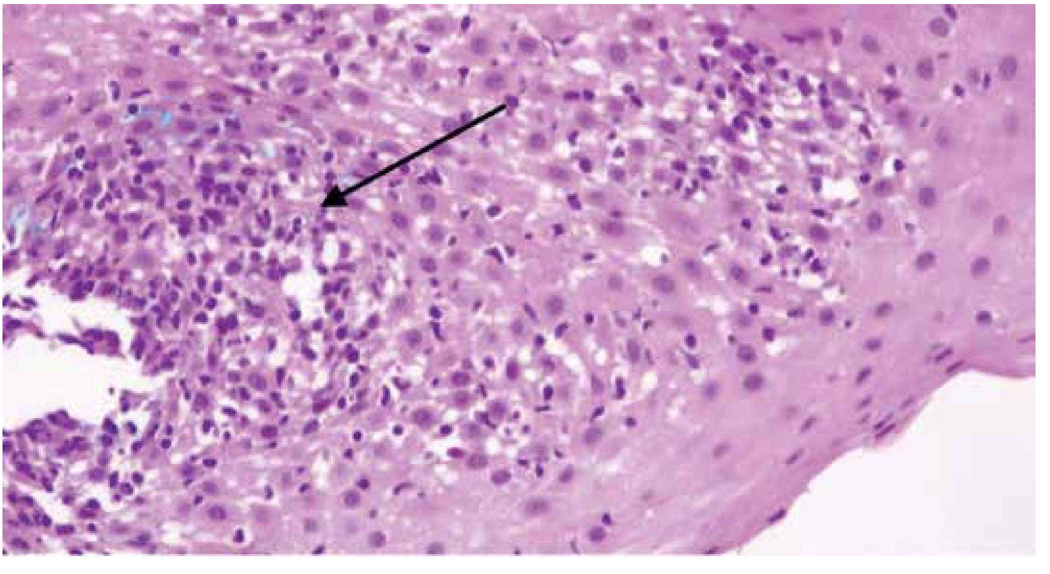

Figure 1. Lymphocytic esophagitic (H&E stain, original magnification ×40). Dense peripapillary lymphocytic infiltrate with spongiosis (arrow). Absence of neutrophils and eosinophils.

Because the lymphocytosis is patchy and uneven, we suggest not to establish a minimum number of intraepithelial lymphocytes [2]. In fact, the various studies about this entity have all used different cutoff, ranging between 10 and 50 lymphocytes per high-power field (HPF) [2, 3, 12, 13].

Furthermore, lymphocytic esophagitis affects the whole esophagus, but predominantly the distal esophagus. Thus, multiple biopsies are necessary to avoid a false negative because the lymphocyte infiltrates are not distributed evenly throughout the entire esophagus [12].

The mucosal involvement is considered mild if the intraepithelial lymphocytosis is only peripapillary and is severe if there is also an interperipapillary lymphocyte infiltration [12].

4. Clinical manifestations

Lymphocytic esophagitis seems to affect mostly women around 60 years old and smokers [2, 3, 10, 11]. The most common symptom is dysphagia [2, 8, 11, 13]. Nausea, vomiting, chest pain, heartburn, and episodes of impactions have also been reported; however, dysphagia remains the principal and most frequent complaint in 53% of cases [2, 3, 12]. Patients with lymphocytic esophagitis do not appear to show weight loss or fever.

The most serious complication is esophageal perforation. In 10 years, two cases of perforation have been reported. One of the two perforations occurred after the removal of a piece of impacted meat, while the second case was a spontaneous microperforation [14, 15].

5. Endoscopic features

Endoscopically, the most frequent findings are a normal esophagus or esophagitis [2, 3, 11]. Up to 33% of cases from the cohort by Haque *et al*. had findings suspicious of eosinophilic esophagitis such as stricture, rings, or felinization without eosinophilic esophagitis on the biopsies [2]. As described later, no other gastrointestinal involvement or association with gastritis or duodenitis has been described, thus stomach and duodenum endoscopic appearance is normal [12].

The endoscopic features are variable and not specific, which makes it impossible to identify and diagnose lymphocytic esophagitis by only relying on symptoms and gastroscopy. It is still a histologic condition, which is why biopsy is essential for the diagnosis.

6. Clinical associations

Some retrospective studies and case reports have tried to identify an association between lymphocytic esophagitis and other clinical conditions. Whether it was inflammatory bowel disease, gastroesophageal reflux disease, celiac disease, asthma, allergies, irritants, or connective tissue diseases (lupus, Behçet's disease), no relationship could be identified [2, 11–13, 16].

Lymphocytic esophagitis is isolated to the esophagus. It does not coexist with other digestive lymphocytosis such as lymphocytic colitis or lymphocytic gastritis. There is no correlation between these distinct entities. In a case series from Purdy *et al*., some patients had concomitant biopsies from the rest of the digestive tract (stomach, small intestine, or colon). The histologic findings in these biopsies were various and secondary to preexisting conditions. No lymphocytic entity was observed in the rest of the gastrointestinal tract [8].

6.1. Gastroesophageal reflux disease

One of the main research efforts was to identify a relationship between lymphocytic esophagitis and reflux. Unfortunately, no association has been established between these two conditions [2, 12]. Indeed, only 22 out of 119 patients in the cohort from Haque *et al*. had gastroesophageal reflux disease [2].

6.2. Crohn's disease

In the cohort from Rubio *et al*., 8 of 20 patients had Crohn's disease [1]. However, subsequent studies failed to replicate this association with inflammatory bowel disease [2, 11, 17]. Nevertheless, while it appears that it is not associated with inflammatory bowel disease in adults, lymphocytic esophagitis may be a manifestation of upper gastrointestinal Crohn's disease in the pediatric population [1, 12, 10]. Indeed, seven out of eight Crohn's disease patients from Rubio *et al*. were pediatric cases. Purdy *et al*. confirmed this association with the pediatric Crohn's disease [1].

6.3. Eosinophilic esophagitis

Eosinophilic esophagitis has also been a subject of study and comparison with lymphocytic esophagitis. The clinical and endoscopic manifestations of lymphocytic esophagitis can be confused with those of eosinophilic esophagitis. It is only histology that allows us to differentiate these two entities. Felinization is not pathognomonic of eosinophilic esophagitis, hence the importance of biopsy [2].

In a recent cohort from Rubio *et al*., out of 311 biopsies with an increased number of intraepithelial lymphocytes, 33 cases were a compound of lymphocytic esophagitis and eosinophilic esophagitis [9]. We can thus ask whether these are two distinct conditions or whether one is the continuum of the other. However, this assumption remains a hypothesis and requires to be studied.

6.4. Motility disorders

Since 2014, an interest for esophageal motility disorders in lymphocytic esophagitis has arisen. Recent studies have demonstrated an association with achalasia and primary esophageal motility disorder (nutcracker esophagus, ineffective esophageal motility, and diffuse spasm) [18].

http://dx.doi.org/10.5772/intechopen.69445

In 2015, Xue *et al*. noticed that esophageal biopsies in patients with primary esophageal motility abnormalities had CD4 + intraepithelial lymphocytosis. Moreover, Xue evoked the possibility of a new clinical entity that they called "dysmotility-associated LE." We still need further studies to better understand and characterize this association [11].

7. Treatment

Treatment of lymphocytic esophagitis remains controversial. Very few studies addressed this subject. Because it is still a recent and rare entity, a majority of therapeutic trials have been reported in the form of case reports or retrospective studies.

Proton pump inhibitor, topical or oral steroids as well as esophageal dilation or injections of Botox have been tried. All these treatments have been partially effective [3, 13–16, 19–21]. Nevertheless, it is too early to establish which treatment is better and should be recommended.

The use of proton pump inhibitor is based on the belief that lymphocytic esophagitis may be associated with esophageal reflux. However, as mentioned earlier, this association remains unclear and unlikely. Nevertheless, given the low toxicity of proton pump inhibitors, we suggest using them as first line of treatment.

Concerning the efficacy of corticosteroids, it may suggest that lymphocytic and eosinophilic esophagitis belong to the same family.

8. Natural history

Unfortunately, we have very little data on the clinical course of this condition. Cohen *et al*. was the only one who studied this sphere through a survey he sent to 29 patients with lymphocytic esophagitis. In his cohort, patients report an improvement in their symptoms with medical treatment (proton pump inhibitor or anti-TNF for Crohn's cases). Control endoscopies were performed in 22 out of 29 patients and 9 esophageal biopsies showed persistence of lymphocytic esophagitis despite treatment [3].

Current available literature points out that lymphocytic esophagitis is a chronic condition [12]. The risk of esophageal neoplasia is still unknown.

9. Conclusion

Lymphocytic esophagitis is a newly described clinical and histologic condition that will probably be increasingly recognized upon the next years. Recent publications have allowed us to establish clear criteria, thus facilitating the diagnosis. Clinicians need to be aware of this entity because lymphocytic esophagitis may eventually be in the diagnostic algorithm of dysphagia.

Pathologists are increasingly recognizing this condition, which is an asset for research. With larger cohorts, we will be able to further characterize its worldwide epidemiology, clinical associations, as well as treatment and natural history. Single-cell analysis of the intraepithelial lymphocyte subtypes may help in understanding the pathophysiology of the condition and compare subgroups with compound eosinophilic esophagitis and those without. As Haque once said, “it is a condition in search of a disease.”

Acknowledgements

We are grateful to Dre Amélie Therrien (Hôpital Saint-Luc, CHUM, Montréal) and Dre Elizabeth Arslanian (Hôpital Saint-Luc, CHUM, Montréal) for the critical review of the manuscript.

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Section 4

Esophageal Tissue Engineering

Tissue Engineering of Esophagus

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69350

Abstract

The incidences of esophageal diseases like atresia, tracheoesophageal fistula, esophagitis, and even carcinoma rise rapidly worldwide. Traditional therapies such as surgery, chemotherapy, or/and radiotherapy, etc. always meet problems, leading to deterioration of the patients' life quality and sometimes the reduced survival rate. Tissue-engineered esophagus, a novel biologic substitute with tissue architecture and bio-functions, has been believed to be a promising replacement in the future. However, the research of esophageal tissue engineering is still at the early stage. Considerable research has been focused on the issues of developing ideal scaffolds with optimal materials and fabrication methods. The *in vivo* tests and clinic attempts are being progressed.

Keywords: materials, scaffolds, fabrication technology, tissue engineering, regeneration

1. Introduction

The incidences of esophageal diseases like atresia, tracheoesophageal fistula, esophagitis, and even carcinoma rise rapidly worldwide. For example, Barrett's esophagus, a complication of chronic gastroesophageal reflux disease (GERD), is a metaplasia of epithelial cells and often causes adenocarcinomas at a rate of approximately 1%. Among them, only 5–10% patients had chance to survive for 5 years if they do not receive treatment at the earliest stage [1]. The atresia of esophagus is a relatively common malformation occurred with a frequency of one in 2500 births [2]. Recently, more than 500,000 individuals are diagnosed with esophageal cancer each year with possibility of 850,000 by 2030 [3]. Esophageal cancer (EC) is a destructive disease. The treatment is usually tough and protracted, so as to inevitably reduce the patients' life quality, and may indirectly contribute to the mortality rate. Badly, the rate of esophageal cancer is 10–100 times higher in Iran, India, Northern China, and Southern Africa than the people in other place of the world [4]. The traditional therapies like surgery, radiotherapy, or/and chemotherapy, and surgically replacing with stomach, colon, small intestine, etc. did not improve greatly the survival rate. In addition, esophagus donor is too rare to get autologous/allogeneic replacement from human body. A tissue-engineered substitute with integrated structure and function is thought to be a promising and effective alternative for treating esophageal disease, which will eliminate the need to harvest replacement tissues from the patients' own body or other human body.

The esophagus is a muscular canal extending from pharynx to stomach and has functions to transport food and water from mouth to stomach. There are three types of cells, i.e., stratified squamous epithelial cells, fibroblasts, and smooth/skeletal muscle cells, which constitute four layers of this tissue, namely the mucosa, submucosa, muscularis externa, and adventitia. **Figure 1** shows the sketch and histological structure of human esophagus, in which a folding lumen is observed in a resting state (**Figure 1a**). The stratified squamous epithelial cells (E) compose the lumen epithelium that serves as a barrier or protective layer against mechanical stresses produced by food bolus. The epithelial cells are supported by the underlying basement membrane (**Figure 1b**, arrows). The topography of the basement membrane is a rugged and uneven stripe that consists of interwoven fibers. The diameters of these fibers were measured to be from 28 to 165 nm with an average of 66 ± 24 nm. The pores displayed between fibers with unequal size (**Figure 1**c). The molecular components of the basement membrane

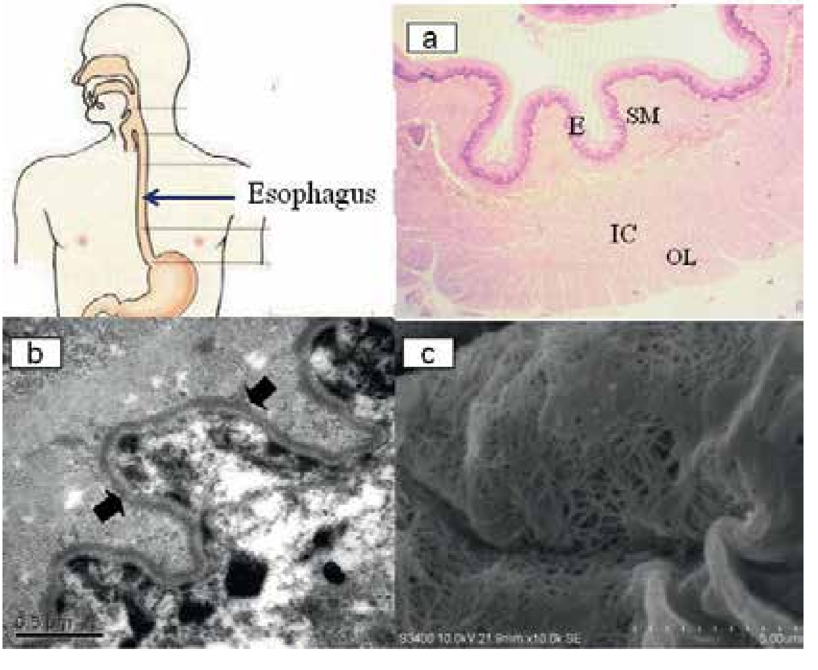


Figure 1. Overview and histological structure of esophagus (a). There are four tissue layers, i.e., mucosa containing epithelium (E), lamina propria and muscularis mucosae, submucosa (SM), muscularis externa consisting of two sublayers of inner circular (IC) and outer longitudinal (OL) muscle, and adventitia in esophagus organ. The stratified squamous epithelial cells (E) lined the esophagus lumen (H&E staining). Cross-section and topography of basement membrane were observed under transmission electron microscope (TEM) (b, c).

http://dx.doi.org/10.5772/intechopen.69350

were detected to be collagen IV, laminin, entactin, and proteoglycans, mainly; among them collagen IV is slightly less than that of laminin but ~50 times more than that of entactin, but the quantity of proteoglycans was ~5 times more than that of entactin [5].

The muscle component in esophagus is responsible for motor function via peristalsis longitudinally and circumferentially. It consists of striated skeletal muscle in upper third, mixture of skeletal and smooth muscle in the middle third, and pure smooth muscle in the lower third. The muscle exhibits a bilaminar arrangement. The endo-circular and exo-longitudinal myofibrils (**Figure 1a**, IC and OL) are packed bilaminarly in order to propel the swallowing food and water into stomach through sequential contraction of the circular muscles via occluding the esophagus lumen, and longitudinal muscle by shortening the duct and enlarging the lumen, or enhancing the fibril density of the circular muscle, which in turn improves the contracting efficiency of the circular muscle [6–8].

Tissue engineering is an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function, proposed by Langer and Vacanti. Scaffolds, cells, and their combination are the main three topics of tissue engineering research. Material is the necessary substratum in scaffold fabrication. There are various types of materials that have been developed as scaffold matrices to constitute esophagus tissue, for example, resorbable substances, decellularized matrices, acellular patches, and the composites from natural and/or synthesized polymers. Among them, a number of tissue-derived extracellular matrix (ECM) like decellularized urinary bladder submucosa, gastric acellular matrix, aortal acellular matrix, acellular dermal grafts, and decellularized esophagus have been much investigated for the applications as esophagus replacement. Some have also been tested for healing injury of esophagus in animal models or even human trials. Alternatively, synthesized and/or natural materials or their composites also attracted more and more attentions in researches of tissue engineering and regenerative medicine. Refs. [9, 10] reported that poly(glycolic acid) (PGA) and silicone with collagen coating were applied to constitute tubular scaffold. Small intestinal submucosa (SIS) was used as the replacement of tubular organs, for example, esophagus and large-diameter vascular grafts, as literature reports. Nonetheless, the complications or postoperative problems like inflammation, leakage, stenosis, and extrusion in long-term implantation are still presented when the materials or scaffolds are implanted into bodies.

2. Materials for scaffold constitution

Since the ancient times, some allogeneic materials have been adopted for medicinal purposes. In the past decades, after the concept of tissue engineering was submitted, many natural and artificial materials were adopted to produce scaffolds. Some achievements have been obtained toward improving tissue regeneration in laboratory scaffold, serving as a temporary platform to support or promote the growth of cells or/and tissues, which is one of the key issues in the research of tissue engineering. For esophagus, a variety of natural or/and artificially synthesized materials have been investigated as scaffold substrate.

2.1. Natural biomaterials

Natural biomaterials, for example, collagen, chitosan, gelatin, decellularized extracellular matrix (ECM), etc., all of which are derived from animal sources, have been widely studied in scaffold constitution, since all these materials possesses good biocompatibility and have bio-specific signals cued from the molecules secreted by the resident cells. Thus, they are believed to be able to direct the *in vivo* remodeling process. These natural materials also have been used in a variety of tissue engineering applications, such as the grafts of heart, heart valve, skeletal muscle, skin, cardiovascular grafts, etc. For the research of esophageal tissue engineering, some ECMs like acellular dermal grafts, gastric acellular matrix, aortal acellular matrix grafts, and decellularized esophagus and urinary bladder submucosa had once been tested to repair esophagus in animal models [11–14]. For example, Marzaro et al. seeded porcine esophageal smooth muscle cells (SMC) on the acellular esophagus aiming at healing the defected porcine esophagus. They got results that SMCs grew on the ECM without obvious inflammation and rejection after implantation for 3 weeks [14].

The research team led by Professor Badylak pioneers the scaffold fabrication using decellularized ECM like porcine urinary bladder matrix (UBM) and small intestinal submucosa (SIS) toward *in vitro* and *in vivo* repairing of esophagus organ [15–17]. For example, they implanted the acellular UBM at the esophagus defects of female mongrel dogs, where the circumferential endo-mucosa/submucosa had been resected. The results showed that complete epithelialization took place on the scaffold surface at day 35, neovascularization and formation of muscle bundles took place at day 50, and the immature nerves and Schwann cells were observed at day 91. After implantation for 230 days, neonatal esophagus with the formation of well-organized tissue laminar and tissue motility had grown [12]. Another important application is skeletal muscle ECM. They decellularized skeletal muscle with enzymes and chemicals to obtain acellular ECM. This ECM was verified to contain the growth factors, glycosaminoglycans, and basement membrane structural proteins. Expectedly, these components greatly promoted myogenic cells' growth and proliferation *in vitro*, and also promoted the myogenesis when the ECM was implanted into a rat abdominal wall. The ECM scaffold was found to degrade gradually at the implant site [16]. The xenogeneic ECM derived from porcine SIS combined with endoscopic technique was adopted to repair dysfunctional esophagus of five male patients who had esophageal adenocarcinoma, Barrett's or/and high-grade dysplasia (HGD). After 24 months, patients restored the mature squamous epithelium and returned a normal diet without significant dysphagia. Unfortunately, among these five patients, some recurred Barrett's esophagus, mainly at the gastroesophageal junction [17]. It was the first and very important report about clinical application of tissue-engineered esophagus in human body. A model of the human esophageal mucosa was reported recently by the MacNeil laboratory [18]. Unlike conventional 2D cell culture systems, they seeded primary human esophageal fibroblasts and epithelial cells in a porcine-derived acellular esophageal scaffold and discovered an esophageal mucosa recapitulation after 20 days. It provided a biologic-relevant experiment model of human esophageal mucosa.

Some literatures reported that three-dimensional biological scaffolds made from nonautologous extracellular matrix (ECM) can act as an inductive template for tissue and organ reconstruction after the ECM was recellularized with autologous stem cells or differentiated cells. This kind of ECM/cells was tried to repair and reconstruct some complex tissues like esophagus, trachea, and skeletal muscle in animal models. Porcine SIS was once attempted to be used as the scaffold by Wei et al., on which the canine oral epithelial cells were pre-seeded before transplantation into animal body followed by suturing across an esophageal gap in the cervical portion (~5 cm). Not only reepithelization but also muscle formation was discovered in the cell-seeded SIS after implantation in animal body for 8 weeks [19]. Urita et al. used the decellularized stomach tissue to evaluate the esophageal mucosa regeneration [13]. Isch et al. implanted a commercial decellularized product, AlloDerm® (LifeCell™), for the esophagoplasty of canine cervical esophagus. Complete epithelialization on the membrane surface was achieved after 2 weeks, without obvious anastomotic fistula or stenosis [20]. Bhrany compared the growth of rat epithelial cells on esophageal ECMs decellularized by deoxycholic acid and Triton X-100. The results indicated that treatment with deoxycholic acid was better than Triton X-100 treatment in epithelium regeneration [11]. Koch et al. decellularized a porcine esophagus and implanted subcutaneously into Sprague-Dawley rats. The decellularized esophagus was shown to maintain its native matrix morphology and extracellular matrix composition [21]. Considering the findings in these literatures, we believed that the decellularized ECM is a good scaffold candidate in esophageal tissue engineering.

Proteins or/and proteoglycans derived from animal ECM are also the important materials that have been actively researched previously. Saxena et al. seeded rat esophageal epithelial cells on the collagen-based scaffolds (OptiMaix-3D001315). After cultured *in vitro*, cells were tested to display positive pan cytokeratin PCK-26 which broadly recognizes the epitopes present in most human epithelial tissues [22]. Qin et al. fabricated a cross-linked collagen-chitosan sponge and implanted into the latissimus dorsi of nude mice after it was preseeded with fetal canine esophageal epithelial cells. Ten layers of mature epithelial cells formed after 2 weeks and the collagen-chitosan implant degraded totally after 4 weeks [23]. Saito et al. implored the feasibility of collagen that used to be the substrate of tissue-engineered esophagus [24]. They constituted an artificial esophagus using collagen sponge together with a latissimus dorsi muscle flap and split-thickness skin and replaced the esophagus of rabbits. Five in 12 total experimental rabbits survived without anastomotic leakage or stenosis. The longest survival period in these rabbits was 16 days.

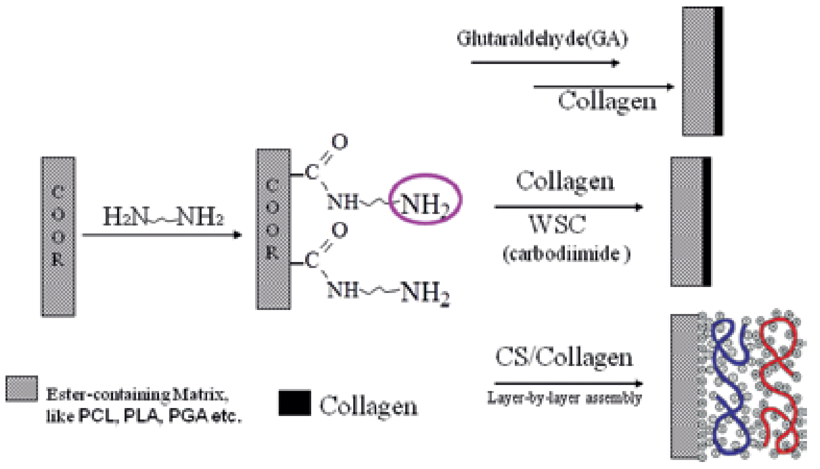
Although many interesting achievements about natural biomaterials have been obtained in some *in vitro* or *in vivo* experiments, problems like weak mechanical strength, fast degradation, and source limitation of these natural biomaterials are still to be worked out.

2.2. Polymeric materials

Artificial polymers have been much investigated as scaffold substrates in tissue engineering because these materials possess many attracting features, for example, good availability, low cost, and high possibility of designing and production. Polyethylene (PE) tube was the earliest example to be an artificial conduit for esophageal replacement in a dog model in 1952 [25]. However, 6 in 20 experimental dogs died after the PE tube was replaced. Leakage and stricture in some dogs were discovered at the site of the PE junction. A fibrous sheath around this plastic tube was developed in all dogs, likely because of the nonbiodegradability of PE materials. Despite the failures, this study is the pioneering experiment of tissue engineering research of esophagus.

Since the concept of tissue engineering was put forward, the interests in using biocompatible and biodegradable polymers, such as polyglycolic acid (PGA), polycaprolactone (PCL), poly-L-lactic acid (PLLA), and their copolymers, has been increasing greatly, particularly after the regulatory approval from the U.S. Food and Drug Administration (FDA). Various kinds of biodegradable polymers have been investigated specifically for the tissue engineering of esophagus. For example, vicryl, made from PGA and collagen coating, is one type of biodegradable and absorbable scaffold with good biocompatibility. It has been tested as a porcine thoracic esophageal replacement in 1991 [26]. No matter what, it failed when the material was implanted into animal body. It was because the reflux gastric fluid dissolved the grafted tube, resulting in severe mediastinitis, leakage, and stenosis. In 1998, Shinhar used vicryl mesh to repair the porcine cervical esophagus. Here, stenosis still took place, though the stump fistula disappeared [27]. Miki et al. fabricated a tube using PGA mesh as a frame, and collagen containing esophageal fibroblasts and epithelial cells as the outer and inner layer, respectively. The fibroblasts were found to be able to accelerate the proliferation and differentiation of epithelial cells due to the keratinocyte growth factor secreted by fibroblasts. After the tube was implanted into muscle flaps of athymic rats for 14 days, nonstenosis was observed in the tube's lumen, but also 20 layers of stratified epithelium were developed from histological examination [28].

One key issue of those synthetic materials used as scaffold matrices is the materials' hydrophobic and biologically inert surface, which will inevitably lead to the inferior reactions between material and cells when the host cells come into contact with the scaffold surface upon implantation. Zhu et al. developed some methods to modify the surface chemistry aiming at enhancing cell-polymer interactions. In order to graft proteins or other biomolecules onto polymer surface, a reaction of ester groups from the substrate polyesters (e.g., PLLA, PU, PCL, and their copolymers) and amino groups (-NH_2) of hexanediamine was firstly introduced to produce pendent amino groups on polyester surfaces through formation of amide bonds. This reaction was called as aminolysis. The density of amino group produced from the aminolysis reaction was quantified using ninhydrin method and fluorescein labeling. Second, this pendent -NH_2 reacted with one aldehyde group (-CHO) from glutaraldehyde (GA). Third, the other aldehyde of GA was used in covalently bond proteins or other biomolecules. Collagen, gelatin, chitosan, fibronectin, polypeptides, growth factors, etc. were thus grafted on the polymeric scaffold surface. Finally, the protein or other biomolecule-grafted surfaces were produced. The water soluble carbodiimide (WSC) can also induce the reaction between the pendent -NH_2 on the aminolyzed surface and –COOH of target proteins, so that the proteins were covalently bonded to the material surface as the **Scheme 1** demonstrated [29–31].The introduction of the amino groups also allows layer-by-layer (LBL) assembly on the polymer surface, because the aminolyzed polyester can be used as a polycationic substratum, on which polyanions can be assembled by means of electrostatic attraction. For example, LBL assemblies of poly(styrene sulfonate, sodium salt) (PSS)/chitosan and chondroitin sulfate (CS)/collagen were performed on the aminolyzed poly-L-lactide (PLLA-NH_2) surface (**Scheme 1**) [32, 33].



Scheme 1. Diagram of reactions between ester groups from synthesized polyesters and amino groups from diamine, aiming at introducing pendent amino groups onto substrate surface, through which many biomolecules containing amino or/and carboxylic groups can be bonded via crosslinking reagents or layer-by-layer assembly technology.

We tried another method, photo-oxidation plus copolymerization, to modify the material surface chemistry. This method was processed under UV initiation to introduce carboxylic groups (-COOH) onto material surface. Through these carboxylic groups, molecules like protein or other bio-molecules (containing COOH) will be bonded onto the surface under the catalysis of 1-ethyl-3-(3-dimethylamino propyl) carbodiimide hydrochloride (EDAC). As a result, covalent immobilization of proteins onto the material surface took place [34]. The optimal conditions for each method with respect to cell functions have been elucidated by *in vitro* evaluation of endothelial cells or esophagus cells including epithelial cell, fibroblast, and smooth muscle cell [30, 35–39].

Another important issue regarding polymers is the catalyst used during synthesis. Those ester-containing polymers are usually synthesized under catalyzing of stannum compounds [40, 41]. However, this kind of catalyst covalently links to the molecular chain of the ultimate products. We know, these stannum-containing materials are harmful to human body when it is implanted *in vivo* as a scaffold substrate, because the bonded stannum will release and accumulate in body as the material gradually degrades. Thus, it is necessary to develop new methods to catalyze efficient polymerizations but no toxicity giving off. Stolt et al. explored the reaction of L-lactide ring-opening polymerization using catalysts generated from iron and acetic acid, isobutyric acid, butyric acid, trifluoroacetic acid, dichloroacetic acid, etc. They discovered that the iron acetate, iron isobutyrate, and iron trifluoroacetate were the efficient catalysts for ring-opening reaction to yield poly(l-lactide) (PLLA) with a molar mass (weight average molecular weight, Mw) of 150 kDa. The monomers' conversion was up to over 85% under the optimum reaction conditions [42]. After this, they produced lactic acid-based poly(ester-urethane) (PEU) using iron monocarboxylates as the initiators, which were prepared from the reaction between iron powder and acetic acid, trifluoroacetic acid, or isobutyric acid. These iron monocarboxylates were considered as catalysts in reactions of hydroxyl-terminated prepolymers and further linking with hexamethylene diisocyanate. The final product, PEU with high Mw, was achieved under the catalyst of fluorinated iron acetate [43]. Zhu group investigated the polymerizing of ester-containing monomers like lactide, caprolactone, glycolic acid, etc. using ferric chloride ($FeCl_3$), ethanol iron ($Fe(OC_2H_5)_3$), iron (III) acetylacetonate ($Fe(acac)_3$), or iron (II) acetylacetonate $Fe(acac)_2$, as the catalyst. The result was that $Fe(acac)_3$ was the most efficient catalyst among them to yield products with high monomer conversion and number average molecular weight [44]. Based on these studies, an oligomer, poly(ethylene glycol-co-lactide) dimethacrylate (PLEGDMA) was further synthesized via ring-opening polymerization of L-LA and polyethylene glycol (PEG) under $Fe(acac)_3$ initiation. After cross-linking with PEG diacrylate and NIPAAm, or with linear prepolyurethane in the homemade mold, biodegradable tubular scaffolds with good mechanical properties were fabricated (**Figure 2**). These scaffolds were verified to be good enough to support the growth of porcine esophageal cells like epithelial, fibroblast, and muscle cell.

3. Fabrication of 3D scaffold for esophageal tissue engineering

Biodegradable 3D scaffolds serve as analogues of extracellular matrix (ECM) in the engineered tissue or organ. Therefore, the scaffold's chemistry and macro and/or microscale architecture must be helpful to maintain cell's functions including cell-matrix adhesion, cell-cell adhesion, cell migration, proliferation, differentiation, etc. On the other hand, 3D scaffold should provide spatial cues for cell infiltration, so that cells are capable of integrating with the underlining substrate. People are always seeking techniques to fabricate spatial scaffolds. Some technologies like foaming, porogen leaching, electrospinning, or other fiber processing, phase separation, 3D microprinting, etc. were developed to construct 3D porous scaffolds. In particular, electrospinning technology and thermally induced phase separation (TIPS) method have been extensively studied to constitute 3D scaffolds in tissue engineering of esophagus.

3.1. Phase separation

Phase separation of polymeric materials is often induced by thermal alteration. That is called thermally induced phase separation, shortened as TIPS. TIPS is one of the most practical

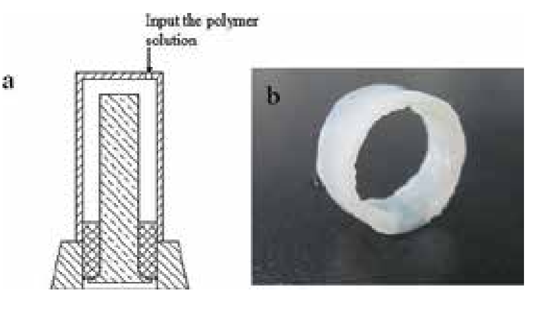


Figure 2. (a) A tubular mold; (b) overview of the tubular scaffold made from crosslinking of PLEGDMA, PEG diacrylate and NIPAAm.

techniques to prepare 3D scaffolds with optimal pore profiles by modulation of process parameters. It was firstly proposed by Castro as early as in 1981 [45] and extended to scaffold making after commencing of tissue engineering [36, 46–48]. The TIPS procedure usually involves four steps: (1) polymer dissolution in some solvent, (2) occurrence of phase separation, (3) polymer gelation, and (4) solvent extraction [49]. There are many advantages of TIPS over other traditional methods such as porogen leaching and foaming. For example, TIPS has the abilities to create a variety of pore structures by employing different parameters, and abroad applications for substrate sources because of its universality for various materials like crystal or noncrystal synthesized polymers [50, 51].

Zhu et al. prepared porous scaffolds with ≥100 μm pore size and good pore interconnectivity using TIPS technique [52, 53]. In order to simulate the ECM architecture, the original TIPS was modified, and thus a scaffold with an asymmetrical pore structure in a hierarchical order was created (**Figure 3**). The pore size on the scaffold surface was small, 1–10 μm, while that of the scaffold bulk was large, ≥100 μm (**Figure 3b**). Primary porcine epithelial cell was cultured on this asymmetrical scaffold lumen surface and primary fibroblast was cultured in the scaffold bulk. The coculture results verified that the bulk with large pores allowed fibroblast migration and infiltration while the lumen superficies with micropores supported the growth of epithelial cells and served as a barrier against fibroblast penetration. The immuno-fluorescent staining (nuclei displayed as blue and keratin as green) of epithelial cells exhibited that several layers of epithelial cells had formed after *in vitro* culture for 14 days on the scaffold lumen (**Figure 3**, **a2** and **b2**). The *in vivo* test showed that a complete layer of epithelium was regenerated on porcine esophagus lumen while the scaffold was being degraded after implantation for 5 months [53].

Beckstead et al. prepared porous sheets with salt-leaching/gas foaming method. The ammonium bicarbonate salt with size from 38–75 to 150–250 μm was used as the porogen reagent. A mixture of 10% chloroform and 90% ethanol was adopted as the polymer solvent. After dissolved in the solvent completely, the polymer solution was evaporated while 50% aqueous citric acid solution was used to initiate gas foaming accompanying with salt leaching [54]. They evaluated the cell (rat esophageal epithelial cell) behaviors on the scaffolds derived from natural material (exemplified AlloDerm), and synthetic materials like poly(lactic-co-glycolic acid) (PLGA) and PCL/PLLA. The results exhibited that AlloDerm scaffold had superior epithelial organization and stratification over other artificial scaffolds. Further modification to the artificial scaffolds would be a necessary way to polish their chemistry and to improve the cell behaviors.

3.2. Electrospinning

The technique of electrospinning was first proposed by Formhals in 1934 [55]. After that, it was gradually applied in diverse regions, for example, filtration industry, wound dressings, controlled drug releasing, and scaffold making in tissue engineering, and so on. In particular, this technique has gained popularity in tissue engineering fields, as a means of making scaffold. The fiber sheets obtained from electrospinning process possesses many features similar to natural ECM, for example, fibers were loosely connected with nano to microscale diameters; the sheet has high porosity and high surface area to volume ratio. Therefore, this technology became an interesting and valuable way to constitute scaffolds for esophageal tissue engineering.

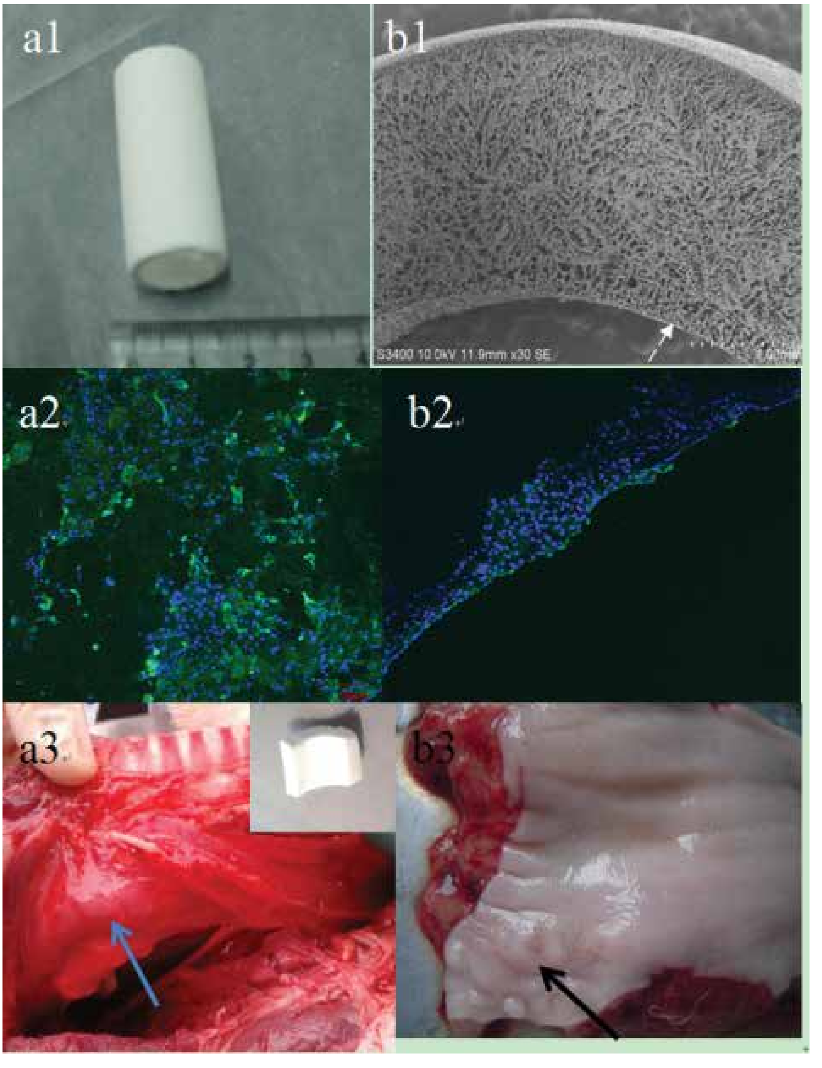


Figure 3. Overview of tubular scaffold (a1) and cross-section structure (b1). The scaffold was prepared with TIPS technique using biodegradable poly(l-lactide-co-caprolactone) as the substrate material. Primary epithelial cells were cultured on the scaffold lumen for 14 days and the immunofluorescence staining (nuclei displayed as blue and keratin as green), a2 is surface scanning and b2 is cross-section observation. The scaffold was surface grafted with fibronectin and implanted in porcine esophagus for 5 months (a3 and b3). Arrows in b1 indicate scaffold lumen, and in a3 and b3 referred the nude esophagus and scaffold-implanted site.

A typical electrospinning setup includes a syringe pump, a metallic collector, and a high-voltage generator. The parameters of this electrospinning system, including process parameters (e.g., electric potential, solution flow rate, distance between the spray nozzle and collector, etc.), polymer solution properties (e.g., solvents, solution viscosity, and concentration), and ambient parameters (e.g., temperature and humidity) influence the fiber features and internal construction.

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Leong et al. yielded poly(D,L-lactide) fibers with the diameter of ~1 μm and nanoscale pores on each fiber through the method of electrospinning combined with phase separation. Large pores between the fibers in the whole sheet were also formed. Such multiporous structure greatly enhanced the cell-matrix interactions and thus promoted the adhesion of porcine esophageal epithelial cells onto the fibers [56].

We have set up a programmable electrospinning system (China Patent ZL 200810062323.8) to upgrade the apparatus's versatility. Besides the basic components, i.e., high-voltage generator and syringe pump, an electronic controller that allows manipulating the nozzle and metallic collector was automatically incorporated into the system. Two nozzles were applied in this system. They can be connected independently to two syringe pumps via silicone tube and operated under programmable monitor to spray polymer fibers individually, sequentially, or simultaneously. Using this upgrade system, a uniform composite fiber sheet consisting of polymers and natural biomaterials with the diameter ranging from 1 to 600 nm was created. These composite sheets derived from proteins and polymers showed good biocompatibility and good mechanical properties. Furthermore, a PCL fiber mesh with macroscopically alignment was electrospun on this setup. The interesting discovery is that this aligned fiber was able to switch smooth muscle cells from synthetic to contractile phenotype and hopefully to maintain the biological function of the cultured muscle tissue [57].

Grafting with ECM molecules is a good way for synthetic scaffolds to improve their bioactivity. For example, poly(L-lactide-co-caprolactone) (PLLC) was electrospun to form fibers. After then, they were grafted with fibronectin in order to promote epithelial cell growth [58]. According to the findings about the topographic features and protein quantifications of the basement membrane of porcine esophagus [4], an electrospun scaffold was fabricated using fibroin (extracted from pregnant silkworm originated in Zhejiang province, China) and polymer as the materials. In order to simulate the architecture of the basement membrane, proteins including collagen IV, laminin, entactin, proteoglycans (PG) extracted from porcine esophagus were coated on the above fibers, aiming at enhancing epithelium regeneration

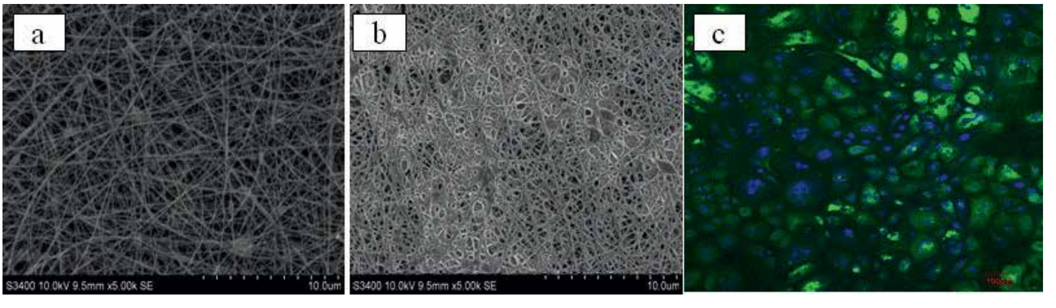

Figure 4. Scaffold morphology of PCL/SF (a), scaffold coated with basement membrane proteins that were extracted from porcine esophagus (b), and cell phenotype immune-histochemically stained with CK14 antibody (green) and nuclei with DAPI (blue) (c).

(**Figure 4**). Silk fibroin is known to have good physical and mechanical properties, and also good biocompatibility. Electrospun fibroin scaffolds together with optimal pore parameters and protein coating extracted from animal esophagus could be great candidates in esophageal tissue engineering [59].

4. Constitution of muscularis propria of the esophagus

The muscle tissue of esophagus consists of striated muscle (skeletal) in the upper third, mixture of skeletal and smooth muscle in the middle third, and pure smooth muscle in the lower third. These muscle contents arrange into endo-circular and exo-longitudinal sub-bilayers to play an important role in propelling the swallowed food or fluid into the stomach via muscle peristalsis. Generating an oriented muscle architecture to mimic the tissue of muscularis externa is an important issue to restore the functions of tissue-engineered esophagus. Many researchers studied the relationship between scaffold's chemistry and microstructure and muscle cells' phenotype. Stegemann once verified that the behaviors of smooth muscle cell (SMC) were positively correlated to the scaffold geometry (2D and 3D) [60]. Li et al. believed that the scaffold geometry played an important role in modulating SMC phenotype. They cultured SMCs and discovered that cells in 3D collagen (type I) gels had lower proliferation and higher collagen synthesis than the cells in 2D collagen substrate [61]. Chan-Park verified that smooth muscle α-actin of SMCs cultured in microchannels upregulated greatly, suggesting a phenotype shift from synthetic to contractile state of cells [62]. They thus believed that 3D microchannels could encourage cells to reorganize into orientation patterns because SMC have a natural self-arrangement propensity. Moreover, the narrow space of channels around 100 μm or less helped cells to achieve more uniform orientation. We also fabricated scaffolds with circular and longitudinal microchannel patterns (**Figure 5**). Further, the scaffold surface was grafted with silk fibroin using our method of diamine aminolysis and GA crosslinking. The primary esophageal SMC was cultured in these 3D protein-grafted channels in order to achieve SMC phenotype regulation and *in situ* muscle formation [63]. The results confirmed that primary esophageal smooth muscle cells exhibited fine alignment in all types of microchannels while SMCs in the interval channels communicated well through the gaps (**Figure 5**).

Some researchers had considered and investigated that mechanical stimulation might be an effective way to regulate SMC phenotype. Ritchie et al. designed a system to exert mechanical forces on esophageal smooth muscle cells. They discovered that cells on the flexile polyurethane membrane displayed alignment parallel to the force direction when low cyclic strains (2%) was used, but alignment perpendicular to the force direction when high strains (5 and 10%) used [64]. Cha et al. reported that muscle cells would orient according to the optimal movement of the tissue. They adopted cyclic mechanical strain (a homemade stretching chamber) on primary myofibroblasts, and promoted the cell differentiation, and further modulated the orientation and proliferation of the differentiated smooth muscle cell. Their conclusion was that myofibroblast/scaffold hybrids with cyclic strain could be applied to organize smooth muscle cells with muscle tissue functions [65].

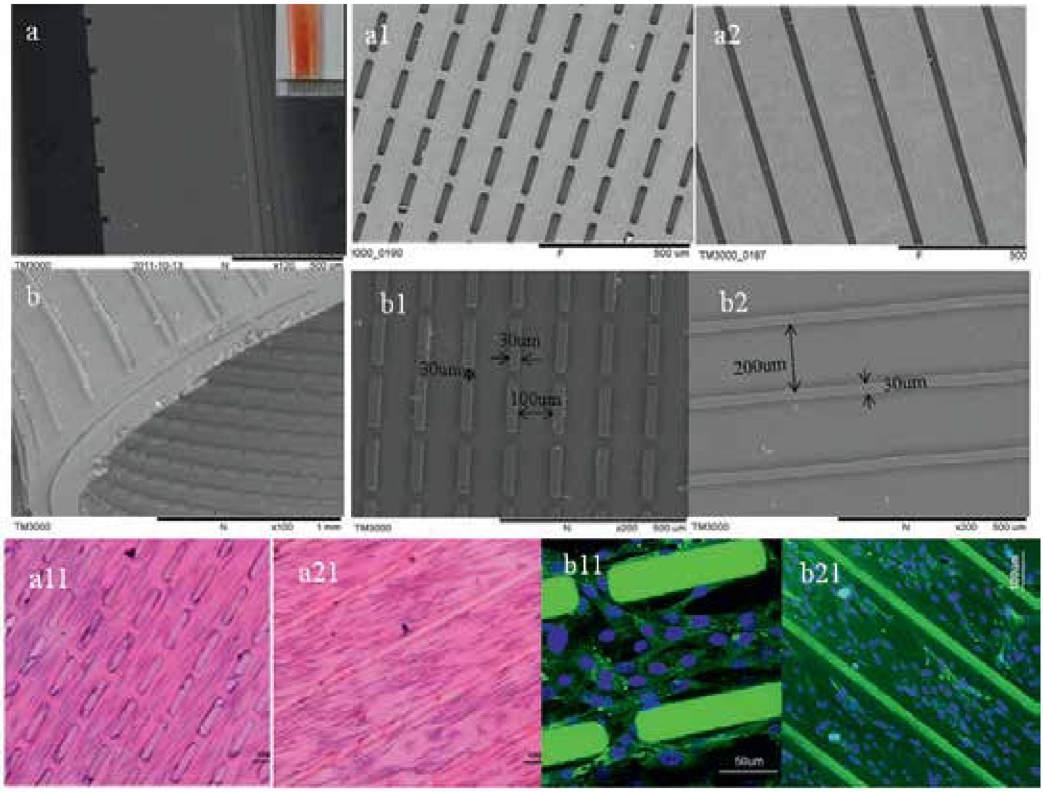

Figure 5. Overview of tubular scaffold (a, inserted) and tube wall's cross-section structure observed under SEM (a). (a1) Scaffold's morphologies of tube lumen and outer face, containing microchannels of 100 μm width with discontinuous channel walls intermitted by 30 μm gap, and both the wall thickness and depth are 30 μm; (a2) microchannels of 200 μm width with noninterval slits. (b) SEM picture of tubular scaffold with bulge wall (b1 and b2). The height of wall and gap between wall intervals is 30 μm. Esophageal smooth muscle cells were seeded and aligned in all scaffolds' channels while cells in the interval channels communicated through the wall gaps (a11, a21 and b11, b21). The scaffold was constructed through silica mold with predetermined patterns using biodegradable poly(ester-urethane) as the substrate material. The surface was grafted with silk fibroin via the method of diamine aminolysis and GA crosslinking. Cells of a11 and a21 were stained by H&E and cells of b11 and b21 were immuno-fluorescently stained with anti-α-smooth muscle as the primary antibody.

5. Clinical potential and future perspectives

With the development of stem cell technology, some kinds of stem cells, for example, embryonic stem cell, mesenchymal stem cell, progenitor stem cell, induced pluripotent stem cell, etc., are adopted to be the seeded cells in tissue reconstruct. In case of esophagus, bone mesenchymal stem cell (bMSC) is more often used to seed on scaffolds than other kinds of stem cells to regenerate or remodel the engineered esophagus. Taylor and Macchiarin reported that allogeneic mesenchymal stromal cells were seeded on the decellularized rat esophagi to orthotopically replace the entire cervical esophagus. After 14 days, the explanted grafts showed regeneration of all the major cell and tissue components of the esophagus including functional epithelium, muscle fibers, nerves, and vasculature. Thus, this tissue-engineered esophageal scaffold was considered as a significant step toward the clinical application of bioengineered esophagi [66].

In summary, the research of substrate materials and scaffold fabrications in esophageal tissue engineering has made great progress in past decades. Esophagus repairs in animal models and even clinical tests are being attempted and the techniques are being improved. Materials with appropriate physical and chemical properties are still being developed. Optimizing scaffolds and cells for epithelium regeneration or/and muscle constitution, and their combination have been in progress. Some crucial problems, such as complications from stricture to dilation, angiogenesis and innervation consideration, little or no muscle regeneration in the implants, etc., need to be issued before the tissue-engineered esophagus can be a viable conduit for surgical replacement in clinic. And, graft-to-host integration and remodeling of the organ functions like peristalsis and nerve guide would be the important gauge for the success in tissue engineering of esophagus. With the development of material science and engineering, stem cell biology, and other related theories and technologies, tissue-engineered esophagus is able to foresee the promising employment in clinic in near future.

Acknowledgements

Financial supports by the National Science Foundation (30870645, 81171476, 81471797) and Scientific Innovation Team Project of Ningbo (2015B11050), China, are gratefully acknowledged.

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Edited by Jianyuan Chai

Human life relies on two basic supplies, oxygen and food. Oxygen can be utilized directly, but food has to go through a long process of digestion to become usable nutrients. The esophagus is the beginning part of this long journey. Because of its critical location, any abnormalities in this part of the body can be devastating and life-threatening and difficult to treat. This book covers many aspects of esophageal disorders, from congenital diseases to cancer. It includes 11 chapters written by highly experienced scholars from all over the world. It is our intention to provide readers an update in esophageal study and to raise the awareness how important this organ to our entire body system.

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