INTRODUCTION

Barrett's esophagus is a premalignant lesion detected in the majority of patients with esophageal and gastroesophageal adenocarcinoma. The progression of Barrett's esophagus may involve the development of low-grade dysplasia and high-grade dysplasia before the eventual development of cancer. Barrett's esophagus is diagnosed in approximately 10–15% of patients with reflux who are undergoing endoscopy ***(Rex et al., 2003).***

BE is the main risk factor for esophageal adenocarcinoma development and its stages of progression from low-grade to high-grade intraepithelial neoplasia and to adenocarcinoma are well established. Risk of adenocarcinoma development in BE patients without dysplasia is 2%. In the presence of lowgrade intraepithelial neoplasia, this risk increases to 7% and high-grade intraepithelial dysplasia, to 22% ***(Steyerberg et al., 2016).***

BE patients periodically undergo endoscopic examinations to detect early dysplastic changes. Treatments currently accepted include clinical treatment with proton pump inhibitor (PPI),endoscopic Ablation through cryotherapy, laser therapy, photodynamic therapy (PDT), multipolar electrocoagulation (MPEC), argon plasma coagulation (APC), and radiofrequency, endoscopic mucosal resection and fundoplication ***(Parrilla et al., 2018).***

Barrett's esophagus is a precancerous state defined by the replacement of normal esophageal squamous mucosa by intestinal metaplasia (IM). The goal of management of patients with BE is to achieve complete eradication of intestinal metaplasia (CE-IM) ***(Cotton et al., 2017).***

To the best of our knowledge, no previous systematic review and meta-analysis has assessed the impact of anti-reflux surgery plus endoscopic resection on the CE-IM of patients with BE.***(Komanduri et al., 2017)*** Therefore, The goal of this meta-analysis study is to detect the efficacy of Nissen's Fundoplication with or without Endoscopic Mucosal Resection in the management of Barretts Oesophagus.

AIM OF THE WORK

The aim of this metaanalysis study is to identify whether Endoscopic Mucosal Resection adds advantage to Nissen's Fundoplication for the treatment of GERD complicated by Barrett's Oesophagus or not.

Chapter 1:

ANATOMY OF THE EOSOPHAGUS

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) ***(Oezcelik et al., 2011).*** 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 27cm by age 10years ***(Kıyıcı, 2011).***

Structure of esophagus

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

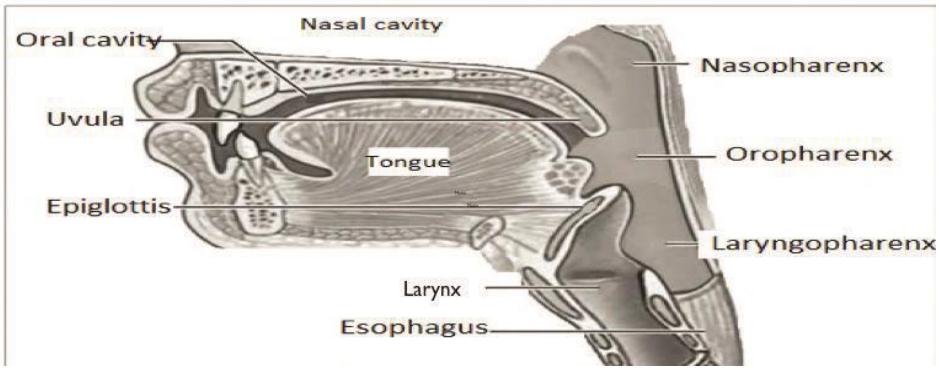

Figure 1: Anatomy of larynx (with permission of Turkish Surgery Association). ***(Oezcelik et al., 2011).***

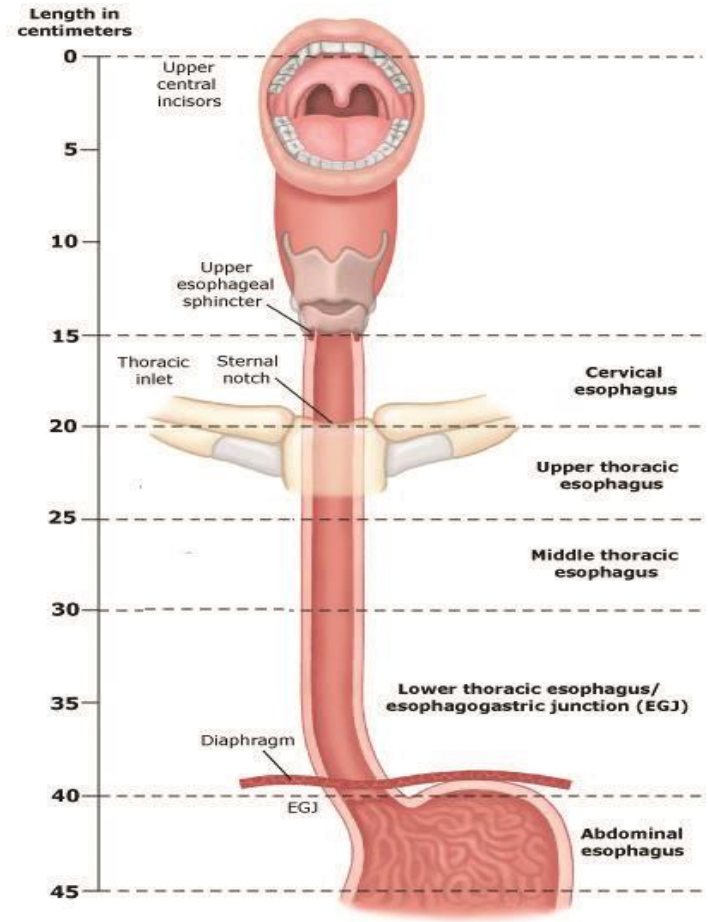

Figure 2: Length of esophageal parts ***(Andrew, 2011).***

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 stratied 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 ***(Minkari et al., 1980).***

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.

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 ***(Floch et al., 2010).*** 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. ***(Floch et al., 2010).*** 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 bers (Aurbach plexus is in this layer) ***(Floch et al., 2010).***

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 ***(Lee et al., 2014)***.

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. ***(Minkari et al., 1980).***

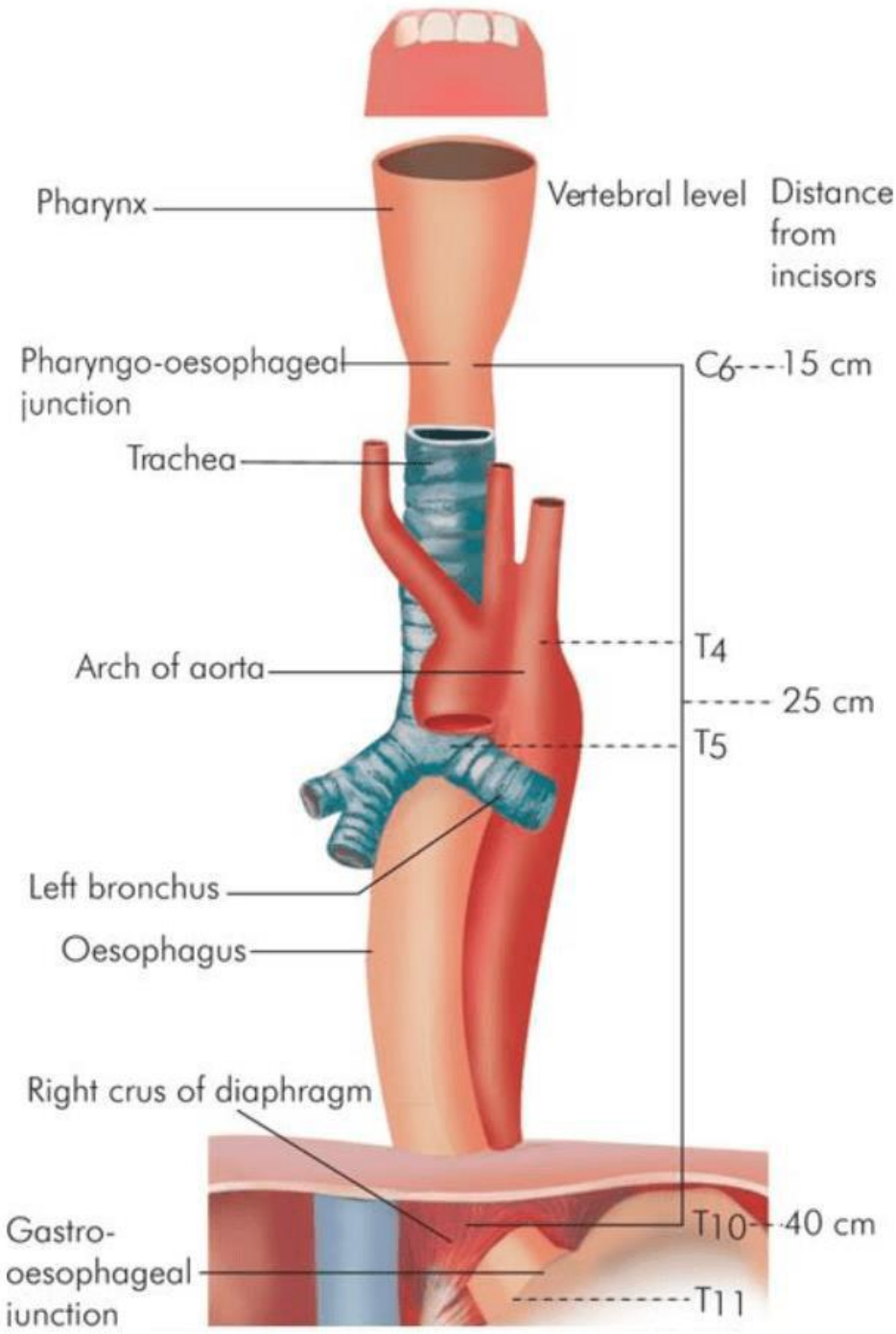

Figure 3: Narrowings of the esophagus ***(Andrew, 2011).***

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." ***(Minkari et al., 1980).*** Second narrowing corresponds to plane that is located at superior border of sternum. Anterior and posterior esophageal walls become closer in hyper extension, 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 ***(Minkari et al., 1980).*** 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. ***(Lee et al., 2014)***. 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.” ***(Lee et al., 2014)***. 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 ***(Lee et al., 2014)***.

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 ***(Minkari et al., 1980).***

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

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," 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 (figure 4) ***(Pope et al., 1970).***

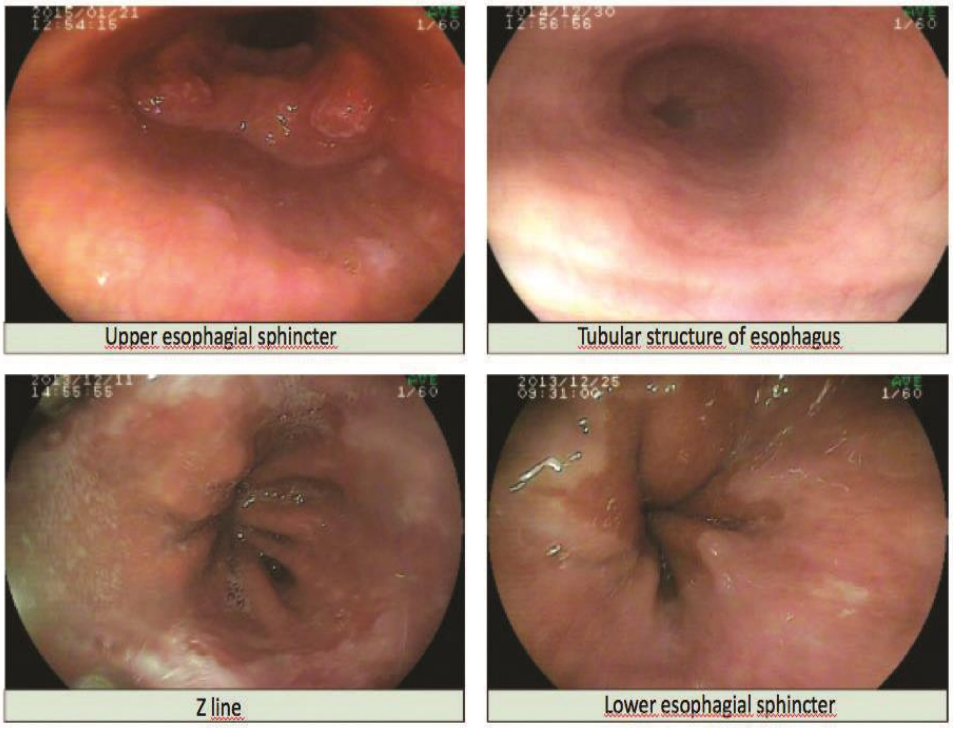

Figure 4: Endoscopic view of esophagus (with the permission of Turkish Surgery Association).

Surrounding structures

Esophagus runs in deepest fascial plane of neck, leaning between trachea anteriorly and vertebra posteriorly. Esophagus is attached to prevertebral fascia by sagital septa, which forms retropharyngeal and retro-esophagial spaces. ***(Skandalakis et al., 2004).***

Esophagus is covered by larynx and trachea anteriorly, but this covering is partial, and an open margin is found on left anterior side, which provides natural surgical access. Esophagus arches 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, thyoid 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 "Pirogo angle," and it makes a slight connection to left side of esophagus ***(Skandalakis et al., 2004).***

Importance of surrounding structures

Sagital 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. ***(McWay and Anson, 1971)***.

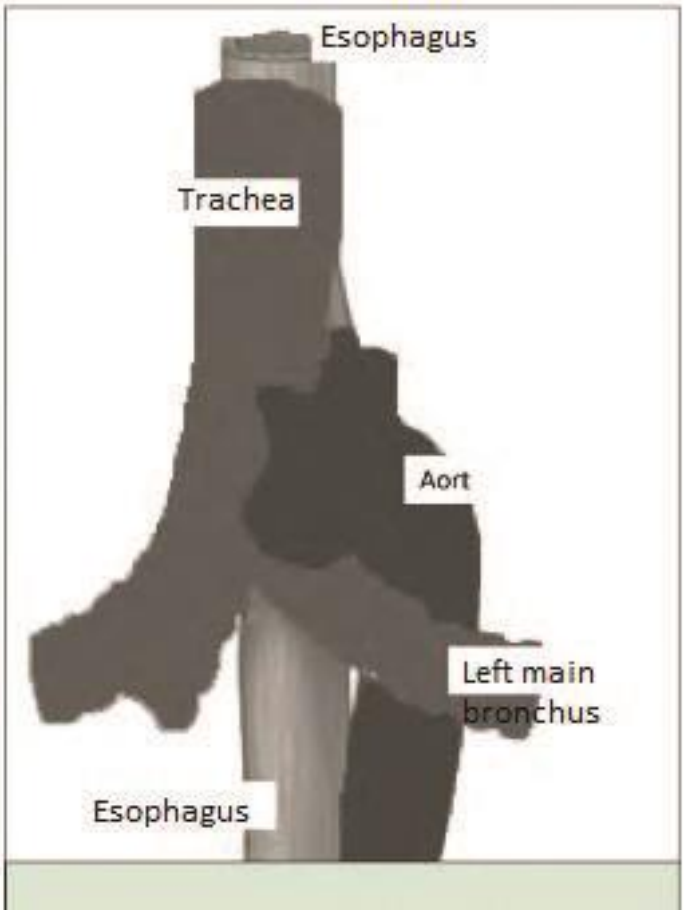

Figure 5: Placement of esophagus relative to other anatomic structures (with permission of Turkish Surgery Association) ***(Helen and Meicker, 1978)***.

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. ***(McWay and Anson, 1971)***. 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 Pirogo 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 ***(McWay and Anson, 1971)***.

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 take the 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 6). Parietal sheet of pleura is tightly connected to both sides of vertebral column, and these connections cause esophageal-