9

Minimally Invasive Esophagectomy for Esophageal Cancer

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Abstract: Esophageal cancer is currently the eighth most common cancer, and the sixth leading cause of death from cancer in the world due to its highly aggressive nature. Better prognosis can be achieved with early diagnosis in early stages of the disease. The increasing incidence rate and the distribution of esophageal cancer varies with tumor type location and with geographical area. Multiple factors like ethnicity, genetic factors, and lifestyle play a role. Currently, Barrett's esophagus is still the only known precursor. Due to its natural history, esophageal cancer is commonly diagnosed in more advanced stages. In tumors confined to the mucosa, local endoscopic treatment is considered curative whereas when the tumor invades the submucosa, surgical esophagectomy is the current standard treatment. In case of locally advanced disease, neoadjuvant chemo or chemo-radio

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therapy is now considered the gold standard treatment. The advent of minimally invasive surgical techniques has reduced morbidity and mortality of esophagectomy without compromising the oncological outcomes. In the chapter, the McKeown mini-invasive esophagectomy technique is described.

Keywords: Barrett's esophagus; esophageal adenocarcinoma; McKeown esophagectomy; minimally invasive esophagectomy; squamous cell carcinoma

INTRODUCTION

Esophageal cancer (EC) is currently the eighth most common cancer in the world and the sixth leading cause of cancer-related death, with a 15–25% five-year survival rate (1–3), due to its highly aggressive nature. Early diagnosis in the early stages of the disease offers better prognosis (2). The incidence of EC has increased by 50% in last two decades with 482,300 new cases diagnosed per year worldwide (4). The increasing incidence and distribution of EC varies with tumor type and with geographical area: squamous cell carcinoma (ESCC) has a higher prevalence in east Asia, southern Europe, eastern and southern Africa, but it has a lower prevalence in north America (4). On the other hand, adenocarcinoma (EAC) is the predominant histological type in the United States, northern Europe, and Australia (2). These geographical variations correlate with the multiple factors that play a role in the origin of EC, that is ethnicity, genetic factors, and lifestyle.

RISK FACTORS AND GENETIC IMPLICATIONS

Several studies have been performed to better understand the etiology and risk factors for EC, and currently Barrett's esophagus (BE) is the only known precursor. BE is a metaplastic transformation from the normal stratified squamous mucosa of the esophagus to a simple columnar epithelium, and its presence conveys a 30- to 40-fold increased risk of developing EAC (5). However, BE is present only in 5% of patients with diagnosed adenocarcinoma (6), so the major challenge is to identify other potential risk factors which include:

Gender and race: There is an increased risk of EAC in people older than 50 years, but no association trend risk per age has been found (7). In white versus black ethnicities the risk of developing EAC is doubled (8). There is also a difference in gender distribution, with a 2-4-fold higher prevalence among males compared to females (9).

Smoking: Smoking is a known risk factor, which is associated with BE and EAC, as well as with ESCC (10, 11), with a higher frequency in men than in women (12).

Gastroesophageal reflux disease (GERD): GERD is the most important risk factor associated both with BE and EAC (13): about 10% of patients with a diagnosis of GERD will develop BE (13, 14), and symptomatic patients have a 5-fold increased risk to progress to EAC as compared to asymptomatic patients (15).

Diet and Alcohol consumption: The reported protective dietary measures against BE (16, 17) are consumption of omega-3-fatty acids, fibers from fruits and vegetables, dietary vitamin C, beta-carotene, and vitamin E. Acetaldehyde derived from alcohol metabolism is the cause of gene mutations, so an alcohol intake exceeding 170 g per week significantly increases the risk of EC (10, 18).

Obesity: Both increased body mass index (BMI) and increased visceral obesity are associated with EC risk, and the risk increases with greater BMI values (19).

Genetics factors: There are genetic conditions related to the development of EC, like Tylosis (*hyperkeratosis palmaris et plantaris*), a genetic autosomal dominant disease associated with a very high lifetime risk of developing ESCC (20). Some genomic mutations are related with EC: a recent large-scale study revealed that more than 83% of ESCCs contained a somatic mutation in TP53 (21). Several other gene mutations, like Cyclin Dependent Kinase Inhibitor 2A (CDKN2A), Retinoblastoma-Associated Protein 1 (RB1), nuclear factor erythroid-derived 2-like 2 (NFE2L2), Checkpoint Kinase 1 (CHEK1), Checkpoint Kinase 2 (CHEK2), Notch homolog 1 translocation-associated (NOTCH1) and Neurogenic locus notch homolog protein 3 (NOTCH3), have been found in ESCC (21, 22). Overexpression of the epidermal growth factor receptor in 59.6–76% of ESCC patients is associated with a poorer prognosis (23, 24). Moreover, other epigenetic alterations, such as DNA methylation, histone modifications, and loss of genome imprinting are related to the development of EC (25).

DIAGNOSIS AND THERAPEUTIC STRATEGIES

Due to its natural history, EC is usually diagnosed at advanced stages. Thus, its early diagnosis would improve treatment outcomes. In patients with BE, annual surveillance by endoscopy should be a standard clinical practice, with random esophageal biopsies performed in all 4 quadrants, each 2 cm of columnar epithelium (26, 27). In the non-dysplastic BE population, the annual cancer risk is very low, ranging between 0.12% and 0.40% per year (28). However, dysplasia without BE increases the risk of cancer at 1% for lesions with low-grade dysplasia and more than 5% for lesions with high grade dysplasia (28), although dysplasia is hardly detectable in asymptomatic individuals. In some areas with high incidence of ESCC, such as northern China, chromoendoscopy techniques could improve the performance of endoscopy and may increase the early detection rate of dysplasia with a cost-effective benefit (29, 30).

The cases of EC detected during screening endoscopy for BE are more likely to have early-stage cancer with longer survival than patients with symptomatic EC (31). However, currently, less than 20% of EC are diagnosed in patients with BE or dysplasia, whereas 80–90% of the total EC are diagnosed in patients with healthy esophageal mucosa (26). When EC is detected at endoscopic biopsy, detailed clinical staging is performed with computed tomography (CT), endoscopic ultrasonography, and positron emission tomography (PET), and tumor staging is based on the 8th edition of AJCC (Tables 1 and 2). In patients with a surgical indication, preoperative workout also includes pulmonary function testing and cardiac evaluation in all cases.

TABLE 1 **TNM classification of Esophageal Cancer from the 8th edition AJCC cancer staging manual (32)**

Category	Criteria
T category	
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades other adjacent structures, such as aorta, vertebral body, or trachea
N category	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph node
N3	Metastasis in 7 or more regional lymph nodes
M category	
M0	No distant metastasis
M1	Distant metastasis

Treatment of early esophageal carcinoma (T1a)

When the tumor does not exceed the submucosa and there is no nodal involvement (T1a, T1b), the tumor is defined as early EC (32). In tumors confined to the mucosa (T1a) the estimated risk of nodal metastases is 1–2%, so a local endoscopic treatment is considered as curative treatment, as well as in case of high-grade dysplasia (Tis) (33, 34). In these cases, the approach should include a combination of endoscopic mucosal resection (EMR) to remove the neoplastic lesion with an ablative technique – like radiofrequency – to manage any residual dysplastic tissue (35). This combined non-invasive treatment modality achieves up to 98% therapeutic efficacy with low morbidity (34, 35). In patients with T1a tumor, esophagectomy is considered as a second option with an outcome that is similar to endoscopic treatment, but it carries a risk of major morbidity, and it should therefore be considered only in patients with a high risk of recurrence, such as in case of multifocal lesions not liable for an ablative treatment (36).

TABLE 2 cTNM staging of Esophageal Cancer from the 8th edition AJCC cancer staging manual (32)

cStage group	cT	cN	cM
Squamous cell carcinoma			
0	Tis	N0	M0
I	T1	N0-1	M0
II	T2	N0-1	M0
	T3	N0	M0
III	T3	N1	M0
	T1-3	N2	M0
IVA	T4	N0-2	M0
	T1-4	N3	M0
IVB	T1-4	N0-3	M1
Adenocarcinoma			
0	Tis	N0	M0
I	T1	N0	M0
IIA	T1	N1	M0
IIB	T2	N0	M0
III	T2	N1	M0
	T3-4a	N0-1	M0
IVA	T1-4a	N2	M0
	T4b	N0-2	M0
	T1-4	N3	M0
IVB	T1-4	N0-3	M1

Treatment of stage I esophageal carcinoma (T1b, N0/N1)

In patients with tumors invading the submucosa (T1b) the rate of nodal metastases exceeds 10% and endoscopic treatment with a curative intent is not feasible (34, 35). According to established guidelines (37–39), surgical esophagectomy is the standard treatment for stage I EC in all histologic subtypes (37–39). Definitive chemo-radio therapy (CRT) may be considered only in patients who decline surgery or those who are not fit for major surgery (37–39).

Neoadjuvant treatment for locally advanced resectable ESCC/EAC (T2/T3)

In patients with locally advanced EC, the long-term outcomes of surgery alone are not satisfactory. Many studies have been conducted to evaluate the efficacy of adjuvant/neoadjuvant therapy, the results being that postoperative chemotherapy only extended the disease-free survival (40, 41), whereas preoperative

neoadjuvant chemotherapy significantly increased the overall survival (42, 43). Based on these trials, preoperative CRT is now considered the gold standard treatment for locally advanced resectable disease, both in Japan and in Western Countries, with recommendations of postoperative CRT in case of nodal metastases at pathologic examination (38, 44, 45). Again, definitive CRT alone may be considered as an alternative treatment in patients who decline surgery or who are unfit for major surgery with curative intent (46), and it is considered the standard treatment for locally advanced unresectable EC (47).

SURGICAL TREATMENT

Surgery has made enormous strides from Torek's first thoracic esophageal resection with extra-anatomic reconstruction with a rubber tube in 1913 (48). The evolution of surgical techniques to replace the esophagus has included three main techniques:

- Ivor Lewis esophagectomy (49): a two-field transthoracic esophagectomy performed through a right or left thoracotomy;
- McKeown esophagectomy (50): a three-field esophagectomy with cervical anastomosis, performed through a thoracotomy, a laparotomy and a cervicotomy;
- Esophagectomy without thoracotomy by Orringer and Sloan (51): a transhiatal esophagectomy without thoracotomy (THE).

Historically, these traditional open esophagectomy (OE) procedures are associated with high morbidity and mortality rates (52, 53) and with an in-hospital mortality rate ranging between 1.2% and 8,8% (53, 54). More accurate patient selection from improved imaging modalities, the advent of minimally invasive surgical techniques and progresses in thoracic anesthesia in the 1990s have drastically reduced the morbidity and mortality rates of esophagectomy without compromising the oncological outcomes. From the first esophagectomy through a right thoracoscopic approach reported by Sir Alfred Cuschieri in 1992 (55) to the current mini-invasive approaches (that include laparoscopic, thoracoscopic, and robotic-assisted techniques), minimally invasive esophagectomy (MIE) has currently become an excellent option for esophageal resection.

Minimally Invasive Ivor Lewis Esophagectomy

Advantages:

- Oncologic "en bloc" thoracic esophageal and gastric lymph node resection;
- Lower rate of anastomotic leak;
- Lower rate of recurrent laryngeal nerve injury.

Disadvantages:

- In the event of anastomotic leak, there may be pleural contamination, with severe morbidity and risk of mortality;
- Access to the chest requires single-lung ventilation, with potentially increased pulmonary morbidity.

Minimally invasive McKeown esophagectomy

Advantages:

- Oncologic "en bloc" thoracic esophageal and gastric lymph node resection;
- Higher lymph node yield and potential for more accurate pathological staging;
- Cervical anastomotic leaks may be managed more easily;
- Preservation of Azygos vein, for surgeons who elect to preserve it (56).

Disadvantages:

- Higher incidence of anastomotic leak;
- Higher incidence of recurrent laryngeal dysfunction and oropharyngeal dysphagia.

Minimally invasive THE esophagectomy

Advantages:

- Elimination of a thoracotomy or thoracoscopy, with reduced pulmonary morbidity and pain;
- Cervical anastomotic leaks may be managed more easily.

Disadvantages:

- Higher incidence of recurrent laryngeal dysfunction and oropharyngeal dysphagia;
- Difficult oncologic "en bloc" thoracic esophageal and gastric lymph node resection.

Outcomes of MIE

The principal complication of MIE continues to be anastomotic leak, with a rate that ranges between 0% and 33% in various series (57, 58). Pulmonary complications also remain a cause of concern. Avoiding a thoracotomy in MIE should decrease this rate, but the reported results are still conflicting (59). The surgical and oncological outcomes, in terms of severity of postoperative complications, perioperative mortality and overall survival, (60, 61), have shown improved results and a proven superiority of MIE, as compared to OE in large-scale studies (60, 61).

MINIMALLY INVASIVE MCKEOWN ESOPHAGECTOMY: HOW WE DO IT

The operation is carried out by two surgical teams, one for the thoracoscopic and cervical steps, and one for the laparoscopic step.

Thoracoscopic step

After induction of general anesthesia with double lumen tube intubation and invasive monitoring lines placement, such as central vein, arterial lines and thoracic epidural catheters, the patient is placed in the left lateral position. Lung is deflated and four port video-assisted thoracoscopy is started. A 10 mm. camera port is placed usually in the VII intercostal space posterior to the mid-axillary line; a 10 mm working port is placed in the 8th intercostal space 4 to 5 cm posterior to the first camera port. Another 10 mm port is usually placed in the fourth intercostal space adjacent to nipple and the last 10 mm port is placed in the sixth intercostal space just beneath the tip of the scapula, that helps in retraction and manipulation for the operating surgeon.

After ports placement, the deflated lung is retracted anteriorly, the area of the tumor is identified and general resectability is assessed. Inferior pulmonary ligament is divided, and the esophagus is exposed after incision of the posterior mediastinal pleura. Medial esophageal dissection is performed first, followed by careful lateral dissection from adjacent aorta. Direct branches from aorta to esophagus are individually clipped or coagulated to avoid troublesome hemorrhage. Azygos vein is usually not divided, but only prepared, encircled and retracted to allow esophageal mobilization and lymphadenectomy. Preservation of the azygos vein is aimed at preventing kinking of the gastric tube that will replace the esophagus. It is critical to stay close to the esophagus to avoid lesions of the membranous portion of the trachea which is closely adjacent. The esophagus is mobilized up to the root of the neck, taking care to avoid injury to nearby major vessels. Adequate lymphadenectomy is performed at this stage. Inferiorly the esophagus is mobilized down to the esophageal hiatus after retracting the diaphragm with a sponge on stick. Hemostasis is ascertained, two closed suction chest drains are placed, followed by closure of the chest cavity, following which the patient is moved to supine position.

Laparoscopic step

Five trocars are used. One 12 mm trocar is placed in supraumbilical position, three 12 mm trocars are placed in the right hypochondrium, left hypochondrium and sub-xiphoid region along the midline, the latter with a longitudinal skin incision. One 5 mm trocar is placed along the left midclavicular line and below the transverse umbilical line. The liver is retracted with a grasper introduced from the subxiphoid trocar. The *bursa omentalis* is opened by dividing the gastrocolic ligament up to its origin from the gastroduodenal artery with an advanced energy device (LigaSure™, Medtronic, Minneapolis, Minnesota, USA or Ultracision, Harmonic Scalpel, Ethicon Endo Surgery, Cincinnati, Ohio, USA) following the course of the right gastro-epiploic arch but avoiding to stay too close to these vessels because it is mandatory to preserve them. Division of the gastrocolic ligament continues on the left until the left gastroepiploic artery is divided at its origin from the splenic artery. Next, the short gastric vessels are divided and the left crus of the esophageal hiatus is exposed. After retracting the gastric body upwards, the gastric coronary vein and the left gastric artery are then prepared posteriorly closed with Hem-O-lok clips (Teleflex Medical Europe Ltd, IDA Business and Technology Park, Dublin Road, Athlone, Co Westmeath, Ireland) and divided. The lesser

omentum is opened, and the abdominal esophagus is separated from the right crus of the esophageal hiatus, followed by division of the phreno-esophageal ligament and complete mobilization of the abdominal esophagus. Abdominal D2 lymphadenectomy is carried out in case of tumors located at the esophago-gastric junction. The cervical stage of the procedure follows thereafter.

Cervicotomy incision

The cervical step of the operation is carried out through a left cervical incision. We use an oblique incision on the left side of the neck after dividing the platysma and dissecting along the anterior border of the sternocleidomastoid muscle. If necessary, the middle thyroid vein is ligated and divided to avoid traction injury near its communication with the internal jugular vein. The strap muscles are divided, and the thyroid gland is retracted medially. The cervical esophagus is exposed, and it is then mobilized and divided using an endoGIA 30 stapler (Medtronic, Minneapolis, Minnesota, USA). An umbilical tape is attached to the distal end of the divided esophagus that will subsequently be pulled down into the abdomen through the esophageal hiatus. The umbilical tape will remain in place through the mediastinum during creation of the gastric conduit.

Abdominal part of the procedure and cervical anastomosis technique

After removing the subxyphoid trocar, a 7–8 cm full-thickness service minilaparotomy is created by prolonging the longitudinal skin incision and an Alexis wound protector device (Applied Medical, California, USA) is positioned prior to esophago-gastric extraction. A narrow gastric tube, measuring 3–5 cm in diameter, is created with a GIA 75 mm linear stapler and green cartridges (Medtronic, Minneapolis, Minnesota, USA) after opening the gastric fundus, evacuating any intraluminal content by gentle suction and inserting a 36 fr calibration tube (Teleflex Medical Europe Ltd, IDA Business and Technology Park, Dublin Road, Athlone, Co Westmeath, Ireland) that is laid along the greater gastric curvature. Four to five cartridges are required to suture and to divide the stomach from the fundus to the antrum along the lesser gastric curvature. The surgical specimen, including the esophagus with tumor and the lesser gastric curvature, are removed and hemostasis of the gastric tube is checked. The right gastric artery is usually preserved in case of tumors located in the thoracic esophagus, otherwise it is divided to remove station 5 lymph nodes if the tumor is located at the esophago-gastric junction. After creation of the narrow gastric conduit, Indocyanine Green Near Infrared Fluoroangiography is performed in order to assess its vascular supply.

The gastric tube is then sutured with two or three silk stitches to the distal extremity of the umbilical tape that followed the esophagus upon its withdrawal through the esophageal hiatus, and it is gently pulled up to the neck by pulling on the umbilical tape from the cervicotomy incision. Particular care is taken at this point to avoid torsion or kinking of the vascular pedicle during this maneuver. Our stapled anastomosis technique aimed at preventing fibrous stenosis of the esophago-gastric anastomosis has been previously described (56). The gastric conduit and the proximal esophagus are then prepared for the anastomosis. The proximal end of the gastric graft is transected, and intraluminal content is

evacuated by gentle suction. Two pexing silk sutures between the posterior wall of the esophagus and the posterior wall of the gastric tube are placed. This allows to maintain the cervical esophagus and gastric tube in a side-to-side position, as a double-barreled gun. In order to avoid mucosal retraction, two full thickness silk sutures are placed on the esophagus and on the gastric wall at the level of the gastrotomy to maintain an adequate traction during the anastomosis. The two forks of an endoscopic linear stapler (ETS45 blue cartridge, Ethicon Endo-Surgery) are placed across the two opposite walls with the anvil on the esophageal lumen side and the cartridge on the gastric conduit side. After approximation of the forks and checking the proximal esophagus to avoid any twisting, the stapler is fired, thus accomplishing the posterior part of the anastomosis. At this time, a nasogastric tube is inserted with its tip brought close to the pylorus, and the anterior aspect of the anastomosis is completed by two or more additional firings of the Endo-GIA stapler straight across the raised edges of the stomach and of the esophagus. If necessary, two or three sero-muscular silk stitches are then placed to reinforce the anterior part of the anastomosis. Vascular perfusion of the anastomosis may be checked again at this point by repeating Indocyanine Green Near-Infrared Fluoroangiography. Once completed, the anastomosis drops back into the thoracic inlet. A drainage tube is inserted in the cervical wound. After checking for hemostasis in the peritoneal cavity and at the trocar sites incisions, another drainage tube is positioned below the left hemidiaphragm exiting through the left hypochondrium skin incision. Standard wounds closure follows.

CONCLUSION

EC is increasing in frequency, and it displays a highly aggressive behavior. Early diagnosis in early stages of the disease would be associated with better prognosis but is still difficult to achieve nowadays. The increasing incidence and distribution of EC varies with the tumor type, tumor location and with geographical area. Multiple factors are recognized to play a role, like ethnicity, genetic factors and lifestyle. The incidence rate significantly increases in black men with smoking and alcohol consumption habits. The only known precursor remains Barrett's esophagus. Local endoscopic treatment is sufficient and curative in tumors confined to the mucosa whereas surgical esophagectomy is the current standard treatment in case of tumors invading the submucosa. Preoperative chemotherapy or chemoradio therapy is the gold standard treatment for locally advanced disease. The advent of minimally invasive surgical techniques has reduced morbidity and mortality of esophagectomy without compromising the oncological outcomes. Today, minimally invasive esophagectomy is the preferred option when the necessary surgical expertise and technological devices are available.

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