*REVIEW*

# Esophageal cancer: A Review of epidemiology, pathogenesis, staging workup and treatment modalities

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## Abstract

Esophageal cancer is a serious malignancy with regards to mortality and prognosis. It is a growing health concern that is expected to increase in incidence over the next 10 years. Squamous cell carcinoma is the most common histological type of esophageal cancer worldwide, with a higher incidence in developing nations. With the increased prevalence of gastroesophageal reflux disease and obesity in developed nations, the incidence of esophageal adenocarcinoma has dramatically increased in the past 40 years. Esophageal cancer is staged according to the widely accepted TNM system. Staging plays an integral part in guiding stage specific treatment protocols and has a great impact on overall survival. Common imaging modalities used in staging include computed tomography, endoscopic ultrasound and positron emission tomography scans. Current treatment options include multimodality therapy mainstays of current treatment include surgery, radiation and chemotherapy. Tumor markers of esophageal cancer are an advancing area of research that could potentially lead to earlier diagnosis as well as playing a part in assessing tumor response to therapy.

**Core tip:** Esophageal carcinoma is a serious malignancy with regards to mortality and prognosis, and is expected to increase in incidence over the next 10 years. Squamous cell carcinoma is the most common histological type of esophageal cancer worldwide but the incidence of esophageal adenocarcinoma has dramatically increased in the past 40 years. Esophageal cancer is staged according to the TNM system. Common imaging modalities used in staging include computed tomography, endoscopic ultrasound and positron emission tomography scans. Current treatment options include multimodality therapy. Including surgery, radiation and chemotherapy. Tumor markers of esophageal cancer are an advancing area of research that could potentially lead to earlier diagnosis.

## INTRODUCTION

Esophageal cancer is considered a serious malignancy with respect to prognosis and mortality rate. Account-

ing for more than 400000 deaths worldwide in 2005[1]. Esophageal carcinoma is the eighth most common cancer, and the sixth most common cause of cancer related deaths worldwide with developing nations making up more than 80% of total cases and deaths[2]. Over 490000 new cases of esophageal cancer were reported in 2005. While many other types of cancer are expected to decrease in incidence over the next 10 years by 2025 the prevalence of esophageal cancer is expected to increase by 140%[1]. According to the National Cancer Institute, in the United States there will be approximately 17990 new cases and 15210 deaths in 2013[3]. Despite many advances in diagnosis and treatment, the 5-year survival rate for all patients diagnosed with esophageal cancer ranges from 15% to 20%[4]. The epidemiology of esophageal cancer in developed nations has dramatically changed over the past forty years. Forty years ago squamous cell carcinoma (SCC) was responsible for greater than 90% of the cases of esophageal carcinoma in the United States. Adenocarcinoma has now become the leading cause of esophageal cancer in the United States, representing 80% of cases[5]. In 1975 esophageal adenocarcinoma (EAC) affected four people per million, in 2001 the rate had increased to twenty-three people per million. Making it the fastest-growing cancer in United States, according to the National Cancer Institute[6]. Considerable differences of incidence of esophageal cancer exist on the basis of geographic and racial differences, which can be linked to differences in exposure to risk factors. This review discusses epidemiology, pathogenesis, etiology and treatment modalities available for esophageal cancer.

## EPIDEMIOLOGY

Worldwide SCC is the most prevalent histological type of esophageal cancer, while in certain developed nations including Australia, Finland, France, United States and United Kingdom adenocarcinoma of the esophagus predominates[7]. Esophageal cancer incidence and histological type is highly variable based upon geographic location. Incidence rates of SCC of the esophagus have been reported as high as 100 cases per 100000 annually in an area referred to as the "Asian esophageal cancer belt" and this region extends from northeast China to the Middle East[8]. In the United States the National Cancer Institute estimates close to 18000 new cases and more than 15000 deaths from esophageal cancer in 2013[3]. From 1975 to 2004, the incidence of EAC among white American males increased by more than 460% and in the same period, the incidence among white American females increased by 335%[9].

## PATHOGENESIS

The two most common histological types of esophageal carcinoma include SCC and adenocarcinoma. Less than 1% to 2% of all esophageal cancers are sarcomas or small cell carcinomas[10]. Rarely lymphomas, carcinoids,

and melanomas may arise in the esophagus.

## PATHOGENESIS OF SCC

SCC is the most common type of esophageal cancer worldwide. The overall incidence increases with age, reaching a peak in the seventh decade. SCC occurs equally as often in the middle and lower esophagus, with an incidence that is three times higher in blacks in comparison to whites[11].

Major risk factors include alcohol consumption and tobacco use. Most studies have shown that alcohol is the primary risk factor but smoking in combination with alcohol consumption may have a synergistic effect and increase the relative risk. The relative risk in men who used both heavy tobacco and alcohol was 35.4 in white males and 149.2 in black males compared to men of the same race and region who were non-smokers or drinkers[12]. The mechanism of how tobacco and alcohol in combination lead to increased risk of esophageal cancer has been extensively studied. Alcohol can damage the cellular DNA by decreasing metabolic activity within the cell and therefore reduce detoxification function while promoting oxidation[13]. Alcohol is a solvent, specifically of fat-soluble compounds. Therefore, the hazardous carcinogens within tobacco are able to penetrate the esophageal epithelium easier[14]. Some of the carcinogens in tobacco include aromatic amines, nitrosamines, polycyclic aromatic hydrocarbons, aldehydes and phenols.

Other carcinogens, such as nitrosamines found in certain salted vegetables and preserved fish, have also been implicated in SCC of the esophagus. The pathogenesis appears to be linked to inflammation of the squamous epithelium that leads to dysplasia and in situ malignant change[15].

## PATHOGENESIS OF ADENOCARCINOMA

Adenocarcinoma of the esophagus occurs in the distal esophagus approximately three-fourths of the time[16] and has a distinct link to gastroesophageal reflux disease (GERD). Untreated GERD can progress to Barrett's esophagus (BE), where the stratified squamous epithelium that normally lines the esophagus is replaced by a columnar epithelium. The chronic reflux of gastric acid and bile at the gastroesophageal junction and the subsequent damage to the esophagus has been implicated in the pathogenesis of Barrett metaplasia[17]. The exact nature of the metaplasia still remains to be determined. Diagnosis of Barrett esophagus can be confirmed by biopsies of the columnar mucosa during an upper endoscopy. According to the requirements set forth by the United States gastroenterology societies, the biopsy specimen should contain the characteristic columnar epithelium metaplasia with goblet cells for a definitive diagnosis. Barrett esophagus incidence increases with age and is uncommon in children. It is more common in men than women and more common in whites in comparison to Asian or African American populations.

Some studies have shown that the risk of adenocarcinoma of the esophagus may be affected by the extent of esophagus lined by esophageal metaplasia[18]. The longer the segment of esophagus affected the higher the risk of adenocarcinoma. However, given the fact that short segment esophageal metaplasia is more common in the general population, many cases of adenocarcinoma occur in patients with short-segment metaplasia. Less than five percent of patients diagnosed with adenocarcinoma of the esophagus had a prior diagnosis of BE[19]. The risk of developing esophageal cancer is 50-100 times more likely in those patients with BE[15]. However, a majority of patients with BE will not develop EAC, the annual risk in patients with BE has been reported as 0.12%[20].

Screening for BE *via* endoscopy is controversial and challenging. Currently no definitive screening protocol has been formulated due to lack of documentation that screening effects EAC mortality. A large number of patients with BE will not have reflux symptoms therefore predicting which patients will have BE prior to endoscopy is very challenging. Despite no definitive data for universal recommendation, most gastroenterological associations consider endoscopic surveillance "reasonable" and "desirable" in patients with diagnosed BE[21]. The primary goal of surveillance is to identify dysplasia before it progresses to an invasive malignancy. Current endoscopic technique consists of four quadrant biopsies taken every 2 cm in the columnar-lined esophagus for histological evaluation. The American College of Gastroenterology has recommendation guidelines for how often surveillance should take place based upon the presence or absence of dysplasia and grade of dysplasia if present. Surveillance endoscopy is recommended every 2-3 years in patients with no dysplasia. In patients with low-grade dysplasia, surveillance is recommended every 6 mo for the first year. If the dysplasia has not progressed in the first year, yearly surveillance is applicable. In patients diagnosed with high-grade dysplasia (HGD), two alternatives have been proposed. One option is to continue intensive endoscopic surveillance every 3 mo until intramucosal cancer is detected. The other alternative is for the patient with HGD to undergo endoscopic mucosal resection[20]. Although the natural history of HGD is variable, > 30% of patients with HGD will develop EAC within 5 years[22]. Due to the high risk of cancer most patients with HGD are evaluated as if cancer is present.

Another risk factor for EAC is obesity, specifically in those individuals with predominately abdominal centered fat distribution. Hypertrophied adipocytes and inflammatory cells within fat deposits create an environment of low-grade inflammation and promote tumor development through the release of adipokines and cytokines[23]. Adipocytes in the tumor microenvironment supply energy production and support tumor growth and progression[22].

Long-term prognosis after resection is better for adenocarcinoma compared to SCC. A study by Siewert *et al*[24]. Of 1059 patients who underwent resection showed the overall 5-year survival rate for the adenocarcinoma group was 47% in comparison to 37% for the group with SCC.

## ROUTES OF ESOPHAGEAL CANCER SPREAD

Prognosis in esophageal cancer is greatly dependent on local invasion as well as spread to regional and distant structures within the body. Esophageal cancer is notoriously aggressive in nature, spreading by a variety of pathways including direct extension, lymphatic spread and hematogenous metastasis. The lack of serosa in the esophageal wall plays an integral role in the local extension of esophageal cancer. With no anatomical barrier, the primary tumor is able to extend rapidly into the adjacent structures of the neck and thorax including the thyroid gland, trachea, larynx, lung, pericardium, aorta and diaphragm[25]. The lymphatic drainage of the esophagus is extensive. It is drained by two separate lymphatic plexuses, with one lymphatic plexus arising within the mucosal layer and a second plexus arising within the muscular layer. A majority of the lymphatic fluid from the upper two-thirds of the esophagus tends to flow upward, and the lymph from the lower third of the esophagus flows relatively downward, but all the lymphatic channels of the esophagus communicate. Therefore, lymphatic fluid from any portion of the esophagus may spread in either direction and spread to the intrathorax or intra-abdomenal lymph nodes[26]. Esophageal cancer also spreads hematogenously,, in order of decreasing frequency, to the liver, lungs, bones, adrenal glands, kidney and brain. This method of spread is more common with more advanced stages of esophageal cancer[27].

## STAGING OF ESOPHAGEAL CANCER

The clinical staging of esophageal cancer is assessed with the widely accepted TNM system developed by the American Joint Committee on Cancer (AJCC). Pretreatment staging of esophageal cancer will directly affect overall treatment options available to each patient and their prognosis, so accurate staging is essential.

T staging of esophageal cancer focuses on identifying the depth of invasion of the primary tumor. A critical aspect of T staging focuses on establishing if the primary tumor has invaded the surrounding mediastinal structures, given that these patients would no longer be considered surgical candidates. Table 1 describes the TNM system, specifically referring to depth of invasion in T staging[28]. This aspect of staging is essential in determining stage-specific protocols for treatment (Table 2[28]). For example, for T3 or T4 tumors the oncology team will use preoperative chemotherapy or combination radiation and chemotherapy in order to render the primary tumor resectable by surgical excision. In contrast, T1 or T2 tumors are treated primarily with surgical resection[29]. Given the importance of T Staging in treatment options

**Table 1  TNM system, specifically referring to depth of invasion in T staging**

| Category | Description |
|----------|-------------|
| Tis | Carcinoma *in situ* |
| T1 | Tumors invade lamina propria or submucosa |
| T2 | Tumors invade muscularis propria |
| T3 | Tumors invade adventitia |
| T4 | Tumors invade adjacent structures |
| N0 | No regional lymph node metastases |
| N1 | Regional lymph node metastases |
| M0 | No distant metastasis |
| M1a, M1b | Distant metastasis |

and overall prognosis, many modalities have been utilized to accurately establish T Stage. These options include computer tomography (CT), endoscopic ultrasound (EUS) and $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG-PET scan)[30].

## T STAGE OF ESOPHAGEAL CANCER

When assessing the esophagus by CT, a basic starting point to consider is the esophageal wall thickness. A wall thickness greater than 5mm is considered abnormally thick[31] given that the distended wall of the esophagus is usually less than 3 mm[32]. Esophageal wall thickness asymmetry is a classic but nonspecific CT finding of esophageal cancer and esophageal wall thickness symmetry should always be considered when evaluating the esophagus by CT. CT has been shown to be less accurate when compared to other assessment modalities such as EUS[33]. CT assessment of the esophagus is also unable to accurately differentiate between T1, T2 and T3 stages of the primary tumor invasion. This information is essential in order to guide stage-specific protocols of treatment. The most useful aspect of CT imaging in determination of T status is evaluating if the primary tumor invades into adjacent structures. Obliteration of the fat planes between the primary tumor and the adjacent structures on CT would establish the primary tumor as a T4 stage cancer. The sensitivity and specificity of CT to detect mediastinal invasion ranges between 85%-100%[34,35]. It should be noted that while obliteration of the fat planes between the primary esophageal tumor and adjacent structures is usually reliable in the establishment of a T4 stage tumor, it can occur in patients with prior radiation therapy or cachectic patients.

EUS is now considered the most accurate imagining modality available to establish T staging of esophageal cancer. In comparison to CT, EUS is more accurate to differentiate between T1, T2 and T3 tumors[36]. In comparing the two imaging modalities, EUS was able to determine the preoperative T stage 76%-89% in comparison to 49%-59% when CT imaging was utilized[37-39]. This differentiation is essential in guiding stage-specific treatment protocols and the overall prognosis. Overall in a study conducted by Rösch[40], EUS was able to correctly stage esophageal cancer 84% of the time, and the

accuracy improved as the T stage of the primary tumor increased. Accuracy ranged from 75%-82% for the T1 disease state to 88%-100% for the T4 disease state[41]. EUS is a useful tool in assessing the extent of disease as well as response to chemotherapy, when the dimensions of the tumor are analyzed as the primary variable. However, EUS is unreliable for staging esophageal cancer after neoadjuvant chemoradiation[42]. Other potential limitations of EUS do exist. With any form of ultrasound the accuracy of the study is operator dependent. Also, in cases of esophageal cancer where the esophageal lumen has been narrowed by strictures or stenosis, it may not be possible to pass the endoscope through to visualize the entire tumor[30].

## N STAGE OF ESOPHAGEAL CANCER

In esophageal cancer, N Staging can be defined by the involvement (N1) or absence of involvement (N0) of periesophageal lymph nodes. Sensitivity and specificity of CT scans to detect periesophageal lymph node involvement depends on the size of the lymph nodes. Most studies, used the common size criteria of 1 cm to define a lymph node as enlarged. Sensitivity was reported as 30%-60% while specificity was 60%-80%[43]. An obvious limitation of CT imaging in the ability to detect nodal involvement, comes from the possibility that a normal sized lymph node may contain metastatic foci without an obvious increase in the size of the lymph node. Also, an enlarged lymph node does not necessarily mean metastasis, given that benign enlargement and inflammation may occur[43]. Accuracy to detect N stage by CT imaging was reported as 46%-58%[39].

EUS has been shown to be more accurate in determining nodal involvement in esophageal cancer, with an accuracy of 72%-80%[44]. Accuracy has increased greatly with the use of EUS in combination with United States guided fine-needle aspiration to evaluate for lymph node metastasis.

FDG-PET has also been utilized in determining nodal involvement in esophageal cancer. Assessment of local and regional lymph nodes for uptake of FDG is difficult to determine given the intense uptake of FDG by the primary esophageal tumor. However, PET is quite useful in detecting distant metastasis, including metastasis to the abdomen and cervical lymph nodes. Sensitivities were reported as high as 90% in distant lymph node metastasis[45].

## M STAGE OF ESOPHAGEAL CANCER

Esophageal cancer is notoriously aggressive and invasive in nature. In fact 20%-30% of patients with esophageal cancer will have distant metastasis at time of initial diagnosis[27]. The presence or absence of distant metastasis will be essential in guiding treatment options and in determining operability. Common sites of distant metastasis include liver, lung and bones[30].

**Table 2  Aspect of staging is essential in determining stage-specific protocols for treatment**

| Stage | Tumor | Node | Metastasis | Therapeutic options |
| --- | --- | --- | --- | --- |
| 0 | Tis | N0 | M0 | Local ablative therapy |
| I | T1 | N0 | M0 | Surgery |
| ⅡA | T2 | N0 | M0 | Surgery |
| | T3 | N0 | M0 | |
| ⅡB | T1 | N1 | M0 | Neoadjuvant therapy with or without surgery |
| | T2 | N1 | M0 | |
| Ⅲ | T3 | N1 | M0 | Neoadjuvant therapy with or without surgery |
| | T4 | Any N | M0 | |
| ⅣA | Any T | Any N | M1a | Chemotherapy or radiation therapy with or without surgery |
| ⅣB | Any T | Any N | M1b | Palliative treatment |

In the classification system of metastasis set forth by the AJCC, distant metastasis can be subdivided into M1a and M1b. Each of these classifications is crucial in determining possible treatment options. M1a includes metastasis to celiac and cervical lymph node groups. This classification is associated with a better prognosis compared to M1b. Patients classified as M1a often times complete a course of neoadjuvant therapy followed by surgical resection. Patients with M1b include those with distant site metastasis. This classification usually carries a worse prognosis given that surgical resection with curative intent is not indicated in these cases[46].

CT is the most commonly used imaging modality to rule out distant metastasis in patients with esophageal cancer. The most common areas of distant metastasis can be quickly assessed using contrast-enhanced CT. Sensitivity for spiral CT to detect masses ≥ 1 cm has been reported as high as 90%[47].

EUS is limited in its ability to assess for distant metastasis. In general, CT or FDG-PET is preferred over endoscopic United States for M staging of esophageal cancer.

FDG PET most distinct role in esophageal cancer staging is in the detection of distant metastasis. In comparison to CT, PET has been shown to be more accurate in detecting distant metastasis[48]. One study showed that PET was able to detect distant metastasis 15% of the time in patients that were believed to only have primary esophageal cancer by other imaging modalities[49]. If present, distant metastasis places the patient in M1b category and surgery with curative intent is no longer recommended. Accurate M staging is imperative in guiding treatment options.

## TUMOR MARKERS

Serum human relaxin 2 (H2 RLN) is made in the corpus luteum of females and the prostate of males. It helps remodel various tissue components such as extracellular matrix, collagen, and matrix metalloproteinase. There is supporting evidence that RLN is a tumor growth factor and has been shown *in vitro* to enhance invasiveness of breast cancer cells. A study measuring RLN levels in patients with esophageal SCC (ESCC) discovered that patients with higher levels of H2 RLN had more distant metastasis, lymph node metastasis, higher clinical stage, and a shorter survival rate. This study demonstrated the possibility of using H2 RLN as a serum prognostic factor for ESCC[50]. A Japanese study, investigated the prognostic value of the tumor marker p53 in ESCC. They observed no correlation between a p53 aberration and any clinical, pathological, or epidemiology of ESCC[51]. Another study investigated the marker gene, WDR66 through genome-wide expression profiling. Other WD proteins have been used as tumor markers in other cancers, such as hepatocellular carcinoma. WDR66 has a higher concentration in ESCC tissue than healthy tissue. WDR66 was found to have a role in the growth, motility, and epithelial-mesenchymal transition of ESCC. Poor survival was noted with high levels of WDR66 in the tumor tissue[52]. In a Chinese study, the gene marker phospholipase A2 group ⅡA (PLA2G2A) was investigated to determine its usefulness as a prognostic factor of ESCC. PLA2G2A catalyzes multiple fatty acids, including arachidonic acid and is expressed in colorectal, pancreatic, prostate, gastric and lung cancer. Low expression of PLA2G2A in tumor tissue correlated to high-grade tumors, metastasis, increased depth of invasion, lymphatic invasion, and poorer overall survival rate[53].

## PROGNOSTIC FACTORS

Platelet count has been used to help determine the prognosis of other cancers because platelets are an integral component of the inflammation processes. Platelet count is inversely related to the cancer prognosis, as in a higher platelet count correlates to a poorer prognosis. The absolute cut off for platelet count as a prognostic factor has been debated. In one study of ESCC, platelet counts were higher in patients with large tumors. It was determined that those patients with platelet counts ≤ 205000 had a better 5-year survival rate than patients with platelets > 205000 especially when nodes were involved[54].

Tumor length is used as a prognostic factor in ESCC but the length cutoff point in predicting survival has been contested. Researchers in China looked at tumor length in the elderly population (over 70 years old) and the cutoff point was calculated to be 4.0 cm. Patients with a tumor length of ≤ 4.0 cm had a better 5-year survival than those with a tumor length of > 4.0 cm, espe-

cially with a T3-4 grade or nodal-negative patients[55].

Cancer causes a hypercoagulable state and this environment encourages tumors to grow and produce more pro-coagulants. D-dimers are the end product of fibrin and fibrinolysis and have been reported to be associated with tumor prognosis, tumor stage, lymph node involvement, and overall survival. One study looked at the plasma D-dimer levels in patients with esophageal cancer before and after surgery as well as patients without cancer. Their research showed that high levels of D-dimers in the pre-operative state correlated with a higher tumor stage and surgery caused more patients to have a hypercoagulable state which shortened their survival time[56].

Nutrition is an important factor that influences patients with esophageal cancer during their perioperative period. Early enteral nutrition was noted to protect the intestinal mucosa, improved the nutritional status, and increased the immune status patients undergoing esophagectomy. Enteral nutrition protected the intestinal mucosa by maintaining the intestinal barrier against plasma endotoxins[57]. Another study looked at immunonutrition in patients with head and neck cancer and esophageal cancer undergoing chemoradiotherapy. Plasma levels of arginine, eicosapentaenoic acid, docosahexaenoic acid, and nucleotides were measured in patients undergoing chemoradiotherapy, who received either an Immune modulating Enteral Nutrition formula (IEN) or an isocaloric, isonitrogenous formula, Standard Enteral Nutrition (SEN). IEN patients had less weight loss, increased antioxidants, and maintained their functional capacities compared to those with the SEN formula[58].

## TREATMENT

Surgery can be a definitive treatment for Tis, T1 and some T2 carcinoma of the esophagus. There is some debate on whether neoadjuvant chemoradiotherapy or surgery be performed first on T2 esophageal cancer because staging difficulties[59]. There are different surgical techniques for esophagectomy but the main two are transhiatal esophagectomy (THE) and transthoracic esophagectomy. THE does not include a thoracotomy and instead the stomach is mobilized from the surrounding omentum and blood vessels through a midline supraumbilical incision during the abdominal phase[56]. The esophagus is removed from a small cervical incision usually on the left side of the neck during the cervical phase. The transthoracic esophagectomy uses the Ivor Lewis method, the McKeown Modification (3 hole approach), or the left transthoracic approach. Surgeons choose the method based on tumor location and size. The McKeown modification is performed more for middle and upper esophageal cancer while tumors in the lower third of the esophagus are best approached using the left transthoracic approach[56]. The abdominal phase of the transthoracic esophagectomy is identical to the THE and the thoracic phase is accomplished with a posterolateral thoracotomy in the fifth intercostals space. The McKeown modification also includes a cervical phase where the proximal esophagus can be anastomosed to the stom-

ach conduit[60].

Another critical component of esophagectomy is the lymph node dissection. There is debate about which surgical approach is appropriate based upon access, adequacy of the lymph node retrieval, and the lymph node dissection[54]. Each surgical technique have different lymph node retrieval rates based on the surgical exposure of open, laparoscopic or laparoscopic assisted surgery. Laparoscopic surgery offers less blood loss and more patient comfort but not as many lymph nodes can be retrieved compared to the open approach. Placement of a thorascopic port has been shown to provide more exposure into the chest cavity allowing for a more thorough dissection. One study looked at the difference between open and laparoscopic THE without a thorascopic port and found that while the open procedure yielded more lymph nodes this did not affect the patient's overall prognosis[61].

The differences between transthoracic and THE have been extensively debated. A meta-analysis of 52 studies was performed in 2011 comparing the 5 years survival, postoperative morbidity and mortality between transthoracic and transhiatal esophagectomy. The analysis showed that transhiatal method is associated with reduced operating time, length of stay in hospital, postoperative respiratory complications, and decreased early mortality. The transthoracic method is associated with fewer anastomosis leaks, anastomotic strictures, and vocal cord paralysis. There was no significant difference between transhiatal and transthoracic method in 5-year survival rates[62]. These findings agree with two previous meta-analysis conducted in 1999 and 2001[63-64]. This data suggest that the outcome of the esophagectomy does not depend on the surgical method chosen but more on the surgeon's and hospital's experience in dealing with these complex oncological cases[65].

Another treatment option for high grade dysplasia is esophageal mucosal resection (EMR) or esophageal mucosal dissection. EMR dissects the esophageal submucosa to better evaluate and stage early carcinoma[66]. It has been suggested the EMR be performed on lesions with a diameter ≤ 2 cm and only occurs in less than one third of the esophageal wall circumference. EMR is used in conjuction with radiofrequency ablation therapy and cryotherapy ablation to eradicate BE[67]. In one trial, EMR with radiofrequency ablation eradicated 90% of dysplasia and metaplasia in patients[68].

One study investigated the hemodynamic changes during surgery between patients who underwent a transthoracic *vs* THE and their post-operative changes. It was found that there was no statistical significance between transthoracic and THE in their intraoperative hemodynamic changes. However more vasopressors were used during surgery in patients with transthoracic esophagectomy due to increased hemodynamic liability[69].

## MEDICAL AND RADIOLOGICAL TREATMENT

Chemotherapy and radiotherapy are other critical modali-

ties of treatment along with surgery and are used either in a neoadjuvant or adjuvant setting. A patient will receive neoadjuvant chemoradiotherapy for either a T3 or N1 stage disease. According to the 2013 National Comprehensive Cancer Network guidelines of esophageal cancer, the triple therapy drug regimen include paclitaxel/carboplatin, cisplatin/fluoropyrimidine, and oxaliplatin/fluorouracil. The recommended dose of radiation is 41.4-50.4 Gy[70]. However, one study proposes using chemotherapy alone to treat patients with locally advanced esophageal cancer. Their results showed less toxicities and no difference in their five-year survival rate[71].

An article from Cancer Control found that in the United States, neoadjuvant chemoradiotherapy followed by esophagectomy for resectable esophageal cancer, had a better survival rate than those patients treated with surgery alone[72]. A meta-analysis comparing neoadjuvant chemotherapy with surgery *vs* surgery alone showed a survival increase for those patients who underwent neoadjuvant chemotherapy *vs* surgery alone[73].

A Japanese study found that patients < 60 years of age with a hemoglobin ≥ 13 g/dL who underwent preoperative chemoradiotherapy, survived longer than those patients who did not undergo treatment. Albumin ≥ 3.5 g/dL was also associated with prolonged survival[74]. Another study recommends that patients with esophageal cancer who are non-resectable or who refuse surgery can still be treated with definitive chemoradiotherapy due to a 2-year survival rate of 40-55%[75]. Another Japanese study found that patients undergoing triple chemotherapy and esophagectomy without the prognostic factors of five or more positive lymph nodes, metastasis to the cervical, mediastinal and abdominal lymph nodes, stage Ⅲ or Ⅳ disease, or intramural metastasis had better recurrence free survival than patients with esophageal cancer and one of the unfavorable prognostic factors[76].

## CONCLUSION

Esophageal cancer is a serious malignancy with regards to mortality and prognosis. It is a growing health concern that is expected to increase in incidence over the next 10 years. SCC is the most common histological type of esophageal cancer worldwide, with a higher incidence in developing nations. With the increased prevalence of GERD and obesity in developed nations, the incidence of EAC has dramatically increased in the past 40 years. Esophageal cancer is staged according to the widely accepted TNM system. Staging plays an integral part in guiding stage specific treatment protocols and has a great impact on overall survival. Common imaging modalities used in staging include CT, EUS and PET scans. Current treatment options include multimodality therapy mainstays of current treatment include surgery, radiation and chemotherapy. Tumor markers of esophageal cancer are an advancing area of research that could potentially lead to earlier diagnosis as well as playing a part in assessing tumor response to therapy.

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