

Advancements in Esophageal Cancer Management: The Path to Improved Outcomes

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ABSTRACT

Esophageal cancer remains one of the most common types of cancer worldwide and is a major public health issue that is predicted to become more prevalent in the coming years. Squamous cell carcinoma and esophageal adenocarcinoma represent the most prevalent types of esophageal cancer. Due to variables including obesity and gastroesophageal reflux disease, the latter is more often seen in developing countries. Factors such as the extent of tumor infiltration, the involvement of lymph nodes, and the existence of metastasis are considered when determining the disease's stage. The staging process guides the decision-making process for choosing treatment approaches. Treatment options include surgery, radiation, chemotherapy, and targeted therapies, with a multidisciplinary approach that may involve endoscopic options and neoadjuvant treatment. As esophageal cancer treatment options, radiation is becoming more and more popular due to its quick technical improvements. However, the role of surgery in superficial cancers is still under debate, and locally advanced cancers are typically treated with a multimodal approach. Targeted therapies and immunotherapy, informed by genomics and molecular biology, offer personalized cancer therapy and new clinical trials. This review focuses solely on the curative treatment pathway and highlight emerging advances in endo therapy, surgery, targeted therapy and combination therapies.

Keywords: Esophageal cancer, Squamous cell carcinoma Adenocarcinoma, TNM staging, targeted therapies, Cryoablation

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INTRODUCTION

Esophageal cancer (EC) ranks as the eighth most common cancer globally, and it is the sixth deadliest form of the disease, making it a significant global health concern. This has a high chronic malignancy and high mortality rate¹. There were an estimated 604,100 new cases of EC globally and 544,100 deaths from this malignancy in 2020. Majority of these were Esophageal squamous cell carcinoma (ESCC- 85%) followed by Esophageal adenocarcinoma (EAC- 14%). If the rates continue this way, 957,000 new cases and 880,000 deaths from esophageal cancer are expected in 2040². As 80% of esophageal malignancies occur in developing nations where ESCC is more prevalent, Squamous cell carcinoma (SCC) continues to be the most common histological subtype globally³. A study published

in 2004 revealed that in the US, 1%–2% of asymptomatic American adults and 10– 15% of those undergoing endoscopies for gastroesophageal reflux disease (GERD) had Barrett's esophagus, which carries an increased risk for EAC⁴. Due to both dysphagia and tumor-induced cachexia, the majority of EC patients exhibit indications of malnutrition at the time of diagnosis⁵. One of the trickiest and most demanding areas of contemporary gastroenterology is treating esophageal cancer. EC is treatable when it is early detected but usually fatal when it is more advanced. Despite notable progress in the diagnosis

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and treatment modalities, the 5-year survival rates for individuals with esophageal cancer have consistently stayed relatively low, fluctuating between 15% and 25% in most patients with better outcomes when diagnosed in early stages than those who present at later stages. Moreover, there have been significant shifts in the epidemiology of esophageal cancer⁶. Four decades ago, squamous cell carcinoma (SCC) accounted for more than 90% of all esophageal cancer cases documented in the United States. ESCC is the predominant histological type globally with high incidence in the developing nations. With the increase in the prevalence of GERD, the incidence EAC has been on the rise in the developed nations. Early detection and treatment of esophageal cancer is crucial to improving one's survival and quality of life⁷. The causes, stages, and possible therapies for esophageal cancer (EC) are examined in this article.

According to previous studies, males are more prone to developing EC, with a reported lifetime risk in the United States of approximately 1 in 127 for men and 1 in 434 for women. The incidence of EC in the United States has generally been steady for a long time, while it has shown a slight decline during the past ten years. The most prevalent form of EC in White people is adenocarcinoma, whereas SCC is more prevalent in African Americans⁸. The incidence of the condition rises with age in both males and females. EC primarily affects older persons because 60% of reported occurrences are in those over 65, and only 12% of cases are detected before age 55⁹. In India, it ranks as the fourth-highest contributor to cancer-related deaths. Esophageal cancer is the most frequently detected cancer type in the regions of Assam, Meghalaya, Mizoram, and Nagaland. Another high-incidence area in the country is the Kashmir valley¹⁰.

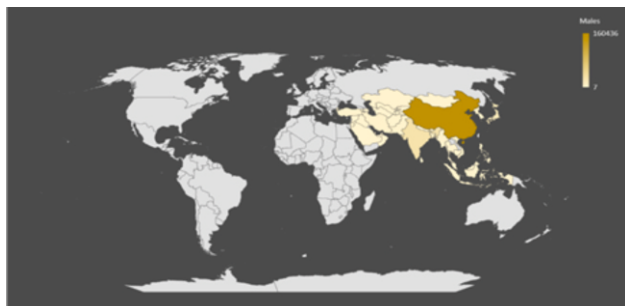


Fig. 1 Epidemiological data for countries in Asia for EC (Males)¹¹

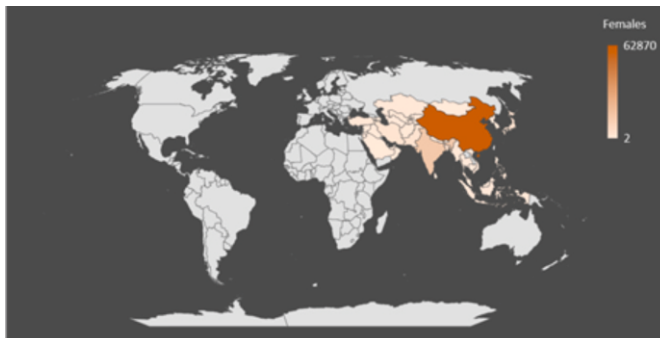


Fig. 2 Epidemiological data for countries in Asia for EC (Females)¹¹

2. Etiopathogenesis

EC has two main types SCC and adenocarcinoma. Sarcomas and small cell carcinomas are rare¹². Risk factors linked to the development of esophageal squamous cell carcinoma include consumption of tobacco, alcohol, hot beverages, and nitrosamines. Additionally, low socioeconomic status, micronutrient deficiencies especially vitamin C, vitamin E, Zinc, selenium and folate have also been linked to the development of esophageal squamous cell cancer. For esophageal adenocarcinoma, apart from tobacco consumption other risk factors include Barrett's esophagus, gastroesophageal reflux disease and obesity. Smoking is a risk factor associated with both Barrett's esophagus and esophageal adenocarcinoma. Alcohol damages DNA and reduces detox function. Tobacco contains carcinogenic compounds that can easily penetrate the esophageal epithelium, including nitrosamines, which is also found in salted vegetables and preserved fish. Inflammation of the squamous epithelium can lead to dysplasia and in situ malignant change, leading to EC^{9, 13}.

Adenocarcinomas generally originate in the area of Barrett's epithelium. The p53 gene has been implicated in a number of human solid tumors, including cancers of the lung and gastrointestinal tract, where it is believed to function as a tumor suppressor gene. The p53 gene may be a broad target for DNA damage in carcinogenesis. Mutations in the p53 cistron, often caused by exposure to UV radiation or other carcinogens, can lead to the development of epithelial cell cancer. In such cases, the mutated p53 cistron is unable to bind to DNA and produce the p21 protein, resulting in uncontrolled cell division and the formation of malignant tumors. While p53 is just one component of the complex process of cancer formation, it is a crucial one that helps to

regulate the cell cycle and prevent the development of neoplasms¹⁴.

2.1 Pathogenesis of Adenocarcinoma

Adenocarcinomas are malignant tumors that develop from glandular tissue in the epithelium¹⁵. Barrett's esophagus (BE), defined as intestinal metaplasia in the distal esophagus, is considered to be a complication of gastroesophageal reflux disease and a precursor lesion in most cases of esophageal adenocarcinoma. Surveillance through upper endoscopy and biopsy are important to detect dysplasia in patients with BE¹⁶. Multilayered epithelium is seen as an initial stage that precedes the development of BE^{17,18}. Somatic genetic alterations occurring in stem cells, along with the presence of an inflammatory microenvironment, are believed to play a role in facilitating the progression from BE to esophageal adenocarcinoma (EAC)¹⁹. Based on results from clinical research^{20, 21, 22} and mice models of BE, the processes by which these variables induce carcinogenesis were evaluated^{23,24}. The Siewert classification is a frequently used anatomical categorization system for gastroesophageal junction adenocarcinomas based on tumor position relative to the gastric cardia²⁵. Indicators for the development of EAC include genetic abnormalities such as chromosomal instability, cell-cycle irregularities, and TP53 and KI67 staining^{26,27,28,29}, as well as mutational inactivation of the p16 and p53 genes, defects in the cell cycle, and aneuploidy³⁰. Previous research showed that people with high abdominal-centered fat distribution are at a high risk of esophageal glandular cancer. Hypertrophied adipocytes associated inflammatory cells inside fat deposits produce an environment of low-grade inflammation and promote tumor development through the release of adipokines cytokines³¹.

Adipocytes in the tumor microenvironment supply energy and promote tumor progression, with shared risk factors and carcinogenic mechanisms observed in both esophageal squamous cell carcinoma and adenocarcinoma despite their histological differences³². Proton pump inhibitors, nonsteroidal anti-inflammatory drugs, and statins, among other medications, influence the risk of BE and the progression to EAC^{33,34,35}. According to epidemiological research, those with *H. pylori* infection have half the risk of EAC and BE as people who may not be infected^{36,37,38,39,40}.

3. Routes of Spread of EC.

EC is regarded for its aggressive action; it can enter nearby, adjacent regions, or far-off regions by a variety of paths, including direct extension, lymphatic dissemination, and hematogenous metastasis⁴¹.

3.1 Spread of cancer by direct extension.

The local spread of EC is significantly influenced by the absence of serosa in the esophageal wall. The thyroid gland, trachea, larynx, lung, pericardium, aorta, and diaphragm are among the nearby components of the neck and thorax that the initial tumor can quickly invade without any anatomical barriers⁴².

3.2 Spread of cancer by Lymphatic spread.

All lymphatic pathways are interconnected to each other. As a result, lymphatic fluid can migrate from one area of the esophagus to another or empty the nodal bed. Cancerous growths from the lower part of the esophagus can extend into the abdominal region. Cancer spread by lymph to the upper and middle gastrointestinal tract can lead to metastasis to celiac to intraabdominal lymph 43. Once esophageal cancer (EC) spreads through the mucosal lymphatic plexus, it can lead to lymphatic metastases or the formation of satellite tumor nodules, which may present as separate implants located at a distance from the primary lesion⁴⁴.

3.3 Spread of cancer by Hematogenous metastasis.

The lymphatic vessels provide a route to nearby lymph nodes, beyond which metastases usually spread through the blood, but the hematogenous system is the main pathway for metastasis to distant organs⁴⁵. In the final phase of EC, this type of cancer becomes apparent. In this, the tumor cell encounters blood and travels to the most common sites' kidneys, bones liver, brain & other major organs⁴⁶.

4. Staging of EC

The TNM system, endorsed by the AJCC, is the standard for staging esophageal cancer, with the 7th edition emphasizing the role of CT, EUS, and PET/CT in initial staging⁴⁷. Nodal participation and the extent of tumor infiltration are the top two crucial prognostic factors for esophageal cancer (EC). The adventitia is involved in T2 tumors, the muscularis propria is involved in T3 tumors, and the neighboring structures are immediately invaded by T4 tumors⁴⁸. Regional lymph nodes (N), metastases (M), original tumor (T), and metastases (M) are the anatomic cancer categories. The Worldwide Esophageal Cancer Collaborative (WECC)

gathered data from 13 institutions spanning five countries across three continents⁴⁹. The 7th edition TNM staging introduced several significant changes compared to the previous editions⁵⁰. According to the 7th edition of the AJCC TNM classification, nonanatomic factors such as histologic subtypes (squamous cell carcinoma and esophageal adenocarcinoma), histologic grade (G descriptor), and tumor location were incorporated into the staging system⁵¹. Since proper staging is crucial for prognosis and management options, the best pretreatment evaluation and stage stratification will enable patients to get the most suitable stage-specific therapy options as shown in Table 1.1⁵²

The 8th edition of the AJCC staging system for esophageal cancer introduced several changes, primarily in the definition of the esophagogastric junction (EGJ) and the categorization of lymph node (LN) metastasis. Specifically, the 8th edition reclassified Siewert type III tumors (those primarily in the proximal stomach) as gastric cancer, whereas the 7th edition classified them as esophageal cancer. Additionally, the 8th edition provides a more refined

classification of lymph node involvement, distinguishing between N3a (7-15 positive nodes) and N3b (16 or more). Detailed definitions of the 8th edition TNM staging can be found in Table 1^{50,53}.

There is a correlation between the T stage and the extent of tumor invasion. The patient's stage, the incidence of metastatic nodal disease, and the outcome are all directly impacted by the T stage (Table 1) of the disease⁵⁴. For T and N staging, endoscopic ultrasonography (EUS) offers a high degree of sensitivity and specificity.⁵⁵ Using fine needle aspiration (FNA), EUS can also be used to assess local lymph nodes and enable N staging. For staging mediastinal lymph nodes and celiac disease, CT scan and PET scan are insufficient^{56,57,58}.

The three main non-invasive techniques for determining the N stage are fluorodeoxyglucose positron emission tomography (FDG-PET), EUS, and CT scan, which allow for regional lymph node imaging. Each test, which indirectly evaluates the possibility that a lymph node may be susceptible to metastases, has limitations specific to that approach⁵³.

Table 1: T, N, and M status and histologic grade definitions for EC

Tumor status	Description
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1 T1a T1b	T1a- Invasion into lamina propria, muscularis mucosae T1b- Invasion into submucosa
T2	Tumors invade muscularis propria
T3	Invasion into adventitia
T4 T4 _a T4 _b	Tumors invade adjacent structures such as the diaphragm, pericardium, pleura Tumors invade unresectable adjacent structures such as the aorta, vertebral body, trachea

Nodal status	Description
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	1 to 2 positive regional lymph nodes
N2	3 to 6 positive regional lymph nodes
N3	7 or more positive regional lymph nodes

Metastasis	Description
M0	No distant metastases
M1	Distant metastases

Histological grades of ESCC and EAC

Histological grades	Description
GX	Differentiation cannot be assessed
G1	Well-differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Assessment of cancer location in ESCC

L category	Description
LX	Location Unknown
Upper	Cervical esophagus to lower border of azygous vein
Middle	Lower border of azygous vein to lower border of inferior pulmonary vein
Lower	Lower border of inferior pulmonary vein to stomach including GE junction

Table 1.1: Therapeutic options according to the staging of EC in determining stage-specific protocols

Stages	Tumor	Nodes	Metastasis	Therapeutic option
0	Tis	N0	M0	Endoscopic resection or Local ablative therapy
I	T1	N0	M0	Surgery (Esophagectomy)
IIA	T2	N0	M0	Surgery, Potentially with neoadjuvant chemoradiation.
	T3	N0	M0	
IIB	T1	N1	M0	Surgery, Potentially with neoadjuvant chemoradiation
	T2	N1	M0	
III	T3	N1	M0	Neoadjuvant chemoradiation followed by surgery or definitive chemoradiation in inoperable patients
	T4	Any N	M0	
IVA	Any T	Any N	M1a	Chemotherapy, radiation therapy, immunotherapy and palliative care
IVB	Any T	Any N	M1b	Palliative treatment

5. Treatment

The treatment of EC has been a challenging task, with surgery showing some progress in reducing mortality rates during the treatment. However, new therapeutic models and technologies have emerged to address this issue^{59,60}. For cancer detected in its early stages, surgery is often the recommended course of treatment. To address BE lesions, different techniques of ablation are utilized, such as laser therapy⁶¹, photodynamic therapy (PDT)⁶², radiofrequency ablation⁶³, argon plasma coagulation (APC)⁶⁴, and cryoablation⁶⁵. EC treatments have limitations, and a combination of surgical and non-surgical therapies is becoming the standard. Due to its immediate benefits, the popularity of minimally invasive esophagectomy (MIE) using thoracotomy is on the rise. Neoadjuvant

chemotherapy (NAC) followed by surgery is the standard for clinical stages II/III, while chemoradiotherapy (CRT) is preferred for patients who refuse surgery or want to preserve their esophagus. A possible alternative to CRT is salvage esophagectomy, but due to the significant morbidity and mortality, physicians are wary. Improving outcomes and developing new approaches are critical for the future⁶⁶. The TNM system is commonly used to stage esophageal cancer, which is essential in determining the appropriate treatment plan as shown in figure 3. The disease's staging is a vital part of care and significantly affects the patient's prognosis.

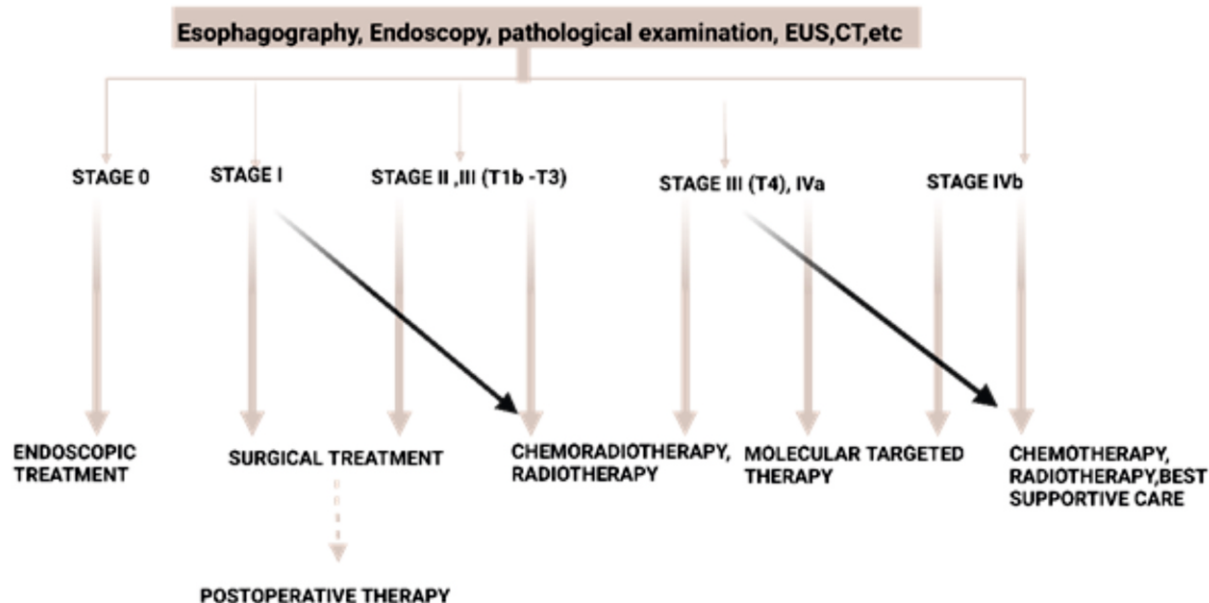


Fig. 3. Defined multimodal therapies for various EC stages.

5.1 Endoscopic treatment

The use of endoscopic resection (ER) has been found to enhance the ability to diagnose early EC. ER can provide precise information on the extent of tumor invasion, helping to distinguish between mucosal and submucosal carcinoma⁶⁷. Therapeutic options for mucosal malignancies encompass procedures such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). The damaged mucosa is excised and removed using a variety of endoscopic electrosurgical blades in the more current ESD procedure. ESD allows for the removal of a more extensive portion of the mucosa in a single, successful procedure. Barrett's carcinoma and other superficial esophageal carcinomas are treated with photodynamic treatment in Western nations. As it is extremely uncommon for lymph node metastases to occur in these situations. In Japan, lesions that are limited to the epithelium, the lamina propria mucosae (LPM), or those that do not infiltrate past the mucosal layer (T1a) are suggested to undergo EMR and ESD. EUS measures the extent of the invasion⁶⁸. The accepted treatment for Stage I ESCC globally is esophagectomy. In the USA, the National Comprehensive Cancer Network's latest guideline (Version 2, 2019) recommends esophagectomy as the standard treatment for cT1bN0 SCC⁶⁹. According to the prior study, when it comes to treating small lesions (less than 10mm) diagnosed as

ESCC, EMR is generally considered adequate. However, for larger lesions, ESD is preferred and considered more ideal⁷⁰.

5.1.1 Photodynamic therapy

PDT is a medical procedure used to treat ESCC. The treatment involves using a photosensitizing drug, which is a medication that has an affinity for cancerous tumors, along with a laser light that triggers a photodynamic reaction. This therapy was originally used to treat cases of superficial ESCC that were difficult to remove using traditional endoscopic methods⁷¹.

5.1.2 Laser therapy

The neodymium: yttrium-aluminum-garnet (Nd: YAG) laser is used to target cancer cells through the tip of an endoscope and eliminate them. While laser endoscopy can be beneficial, cancer recurrence is common, requiring the procedure to be repeated⁷².

5.1.3 Radiofrequency Ablation

Radiofrequency ablation is a modern method of ablating the surface layer of the esophagus, where BE is usually found, using thermal energy. It offers an advantage over older techniques like PDT as it is more precise and controlled, targeting a specific depth. However, a disadvantage of this technique is that it does not provide tissue confirmation of the ablated epithelial lining⁷³.

5.1.4 Argon plasma coagulation (APC)

Some previous researches have shown that APC can be an effective treatment for managing BE 74, Barrett's EC 75, and early gastric cancer^{76,77}. However, there has been a limited evidence on the use of APC in patients with superficial ESCC (SESC)^{78,79}.

5.1.5 Cryoablation

Cryotherapy is a technique that involves using extremely low temperatures to damage tissues, achieved through the rapid cooling, and thawing of the affected area using a cryogen, which is usually a liquefied gas like nitrogen or nitrous oxide⁸⁰. Prior studies on the effects of cryotherapy on the esophageal area were carried out in the 1980s. The study involved using a cryoprobe in direct contact with the esophageal mucosa, which resulted in unpredictable levels and degrees of tissue ablation. The use of this technique occasionally led to esophageal perforations⁸¹.

5.2 Surgery

The primary approach for treating EC is through surgical removal, with curative resection being the most crucial type of surgery. Consider an extended esophagectomy together with a three-field lymphadenectomy for the best results since it delivers improved tumor removal and higher patient survival rates⁶⁸. Currently, surgical intervention for cervical esophageal carcinoma is limited to cases in their early stages, and it requires a significant amount of healthy esophagus upstream of the affected area to be available for reconstruction following the removal of the lesion⁸². EC types T1, T2, and Tis are sometimes treated with surgery, although there is some disagreement on whether neoadjuvant CRT or surgery should be done first on T2 tumors. Transhiatal and transthoracic esophagectomy are the two main surgical techniques that are regularly used; the choice of route depends on the location and size of the tumor⁸³. A two-step treatment known as a transhiatal esophagectomy involves making an incision through the abdominal hiatus and another one in the neck. The cervical incision is used to remove the upper part of the esophagus, while the abdominal incision allows for the creation of a tube-shaped stomach. The stomach tube is then moved through the hiatus and up to the neck, where the esophagus and stomach are joined together⁸⁴. The standard method for doing a transthoracic esophagectomy entails starting with a laparotomy, going to the right thoracotomy, and creating an

intrathoracic anastomosis. This method is known as the Ivor Lewis operation. This method was first described in 1946⁸⁵ and is considered the standard approach for comparison to other techniques. Although the lower part of the esophagus can be accessed by a left thoracotomy or thoracoabdominal incision, doing so can make it more difficult to reach the higher and middle segments and perform a high-chest anastomosis⁸⁶. The development of robotic surgical systems was motivated by the need to overcome the technological limitations of conventional minimally invasive surgery. Robotic-assisted MIE (RAMIE), a technology that was established in 2003, has been described in several case studies as a safe choice with positive oncological outcomes. The RAMIE and open thoracic esophagectomy (OTE) procedures were compared in the ROBOT study, a single-center, randomized controlled experiment⁸⁷.

5.3 Medical and radiation therapy

Esophageal cancer (EC) can be treated with external beam radiation therapy using a variety of techniques, including volumetric modulated arc therapy (VMAT), proton therapy, intensity-modulated radiation therapy (IMRT), and 3-dimensional conformal radiation therapy (3DCRT)⁸⁸. Radiation procedures have improved, resulting in better accuracy, consistency, less damage to healthy tissues, and quicker treatment times. These cutting-edge methods have demonstrated positive results, with improved prognoses and fewer negative consequences. Radiation dosages more than 50 Gy are used to obtain improved local control and survival rates. In addition, an integrated boost strategy is intended to increase radiation exposure to the main tumor while reducing exposure to adjacent subclinical regions⁸⁹. Along with surgery, chemotherapy, and radiotherapy are other essential treatment modalities that can be applied either neoadjuvant or adjuvant. According to the 2013 guidelines from the National Comprehensive Cancer Network (NCCN), the recommended triple chemotherapy regimens for esophageal cancer include combinations such as paclitaxel with carboplatin, cisplatin with a fluoropyrimidine, and oxaliplatin with fluorouracil. The advised radiation dose is between 41.4 and 50.4 Gy⁹⁰. However, one study suggests treating individuals with locally advanced EC with chemotherapy alone⁹¹. Consider treatment alternatives including endoscopic mucosal resection, endoscopic submucosal dissection, or a combination of radiofrequency ablation, according to

advice given to patients with early-stage esophageal cancer (pTis-T1aN0). Surgical resection is recommended for patients with non-cervical segment cancer of the pT1b-2N0 stage. Endoscopic resection (ER) and radiation together can help cure cancer completely and successfully. Radical concurrent CRT is feasible for stage I ESCC. Surgery is the primary therapy for individuals with locally progressed and resectable EC. The treatment approach differs for ESCC and EAC in patients with cT1b-2N+ or cT3-4a N0/N+⁹².

5.4 Molecular Targeted Therapy

In molecular targeted therapy, the molecular targets for the treatment of EC are EGFR, HER2, VEGF, PD-1/PD-L1, and CTLA4. The progress of EC is discussed below sections.

5.4.1 Epidermal Growth Factor Receptor

The EGFR is a member of the ErbB family of receptor tyrosine kinases (RTKs). The attachment of the epidermal growth factor (EGF) receptor's ligand causes the production of homodimers or heterodimers, which in turn causes the receptor to become autophosphorylated. On the other hand, unregulated EGFR activation, such as receptor overexpression and heterodimerization of ligand-dependent receptors, is also significant to the progression of cancer⁹³. The neoplastic progression to EAC has been demonstrated to be significantly mediated by EGFR. It has been the focus of research for specific molecular targeted therapies since it is crucial to the development of EAC tumors⁹⁴. EGFR-targeted treatments fall into two broad categories. The extracellular domain of the receptor is the target of the first group of monoclonal antibodies, including cetuximab and nimotuzumab, which are made to specifically prevent ligand binding and activation. Small-molecule tyrosine kinase inhibitors (TKIs), which focus on the intracellular domain of the receptor, fall under the second group. Examples of these TKIs are gefitinib and afatinib⁹⁵.

5.4.1.1 Anti EGFR Monoclonal Antibodies

The FDA has presently granted permission for the use of the monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer in individuals with wild-type KRAS⁹⁴. As a result of its high affinity for the EGFR, cetuximab suppresses intracellular signaling via inhibiting tyrosine kinases, competitively blocking ligand binding, and causing cell apoptosis while improving

antibody-dependent cytotoxicity^{96, 97}.

5.4.1.2 Small Molecules Tyrosine Kinase Inhibitors

A special kind of targeted treatment known as small molecule tyrosine kinase inhibitors binds to the intracellular ATP-binding site of EGFR and other tyrosine kinase receptors competitively⁹⁸. Gefitinib is an EGFR-TKI that is a selective and reversible agent. It can inhibit ATP binding to the EGFR-TK activation site and inhibit the downstream signals from the receptor from being transmitted, resulting in an anti-apoptotic effect⁹⁹.

5.4.2 Drugs Targeting Human Epidermal Growth Factor Receptor-2(HER-2)

HER-2 is a tyrosine kinase that localizes to cell membranes and carries out extracellular-intracellular signaling to control cell proliferation and differentiation as well as the formation of cancer. It is a member of the EGFR family^{100,101}. One of the current standard therapies for advanced EC is trastuzumab, a genetically engineered humanized monoclonal antibody that binds only to the HER2 protein's extracellular region. It is a novel enzyme-cleavable linker, and a topoisomerase I inhibitor makes up the antibody-drug compound^{102,103}. Trastuzumab has been shown in clinical trials to slow the growth of cancers that express the HER-2 gene¹⁰⁴. A different humanized monoclonal antibody that focuses on HER2 and has been specifically engineered to prevent HER2 dimerization is pertuzumab. Pertuzumab achieves this by attaching to a unique site on the extracellular domain of HER2¹⁰⁵. When coupled with trastuzumab, preclinical trials have shown synergistic anticancer efficacy^{106,107}. In EAC cells that acquired resistance to trastuzumab and pertuzumab, because of activation of the transforming growth factor (TGF)-signaling pathway. Consequently, utilizing medications that inhibit the TGF-signaling pathway may enhance the antitumor action of trastuzumab and pertuzumab¹⁰⁸.

5.4.3 Vascular Endothelial Growth Factor

Vascular endothelial growth factors (VEGF) and their associated receptors, VEGF receptors (VEGFR), interact to regulate angiogenesis in a major way. These interactions are crucial for the development and spread of tumors^{109,110,95}. A monoclonal antibody called bevacizumab binds to VEGF-A and stops it from interacting with VEGF receptors. Bevacizumab selectively targets one of these receptors, the vascular endothelial growth factor receptor (VEGFR).

Through binding to VEGFRs (VEGFR1, VEGFR2, and VEGFR3), VEGFs are released by tumors or stromal cells and act in an autocrine or paracrine way¹¹¹. The extracellular regulated protein kinases 1/2 (ERK1/2) and the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathways can both be activated by the binding of VEGF to VEGFR. This activation speeds up procedures like cell migration, proliferation, and survival^{112,113}. A monoclonal antibody that targets VEGF-A is bevacizumab. For the treatment of several solid tumors, such as metastatic colorectal cancer, glioblastoma, non-small cell lung cancer, and cervical cancer, it has been approved by the FDA¹¹⁴. Bevacizumab is not recommended for the routine treatment of esophagogastric adenocarcinoma during surgery because of its adverse effects on wound healing. A more recent IgG1 monoclonal antibody that targets VEGFR-2, ramucirumab, has shown strong efficacy in preclinical studies¹¹⁵.

Ramucirumab's adverse effects include myelosuppression, rash, thrombosis, hypertension, and thromboembolism¹¹⁶. The VEGF-2 small molecule inhibitor apatinib is extremely selective. Its effectiveness in treating individuals with advanced, chemo-resistant EAC was assessed in a recent

phase III trial. According to a clinical research, apatinib may be used as a secondary or tertiary therapy for advanced ESCC¹¹⁷. The general EAC therapeutic paradigm appears to include VEGF-targeted therapy¹¹⁸.

5.4.4 PD-1/PD-L1-Targeted Therapy

It is thought that the programmed cell death protein 1 (PD-1) pathway plays a significant role in inhibiting the failure of T cells. PD-L1, one of PD-1's ligands, has been found in a number of cancer cell types, demonstrating that cancer cells are capable of evading the immune system's damaging ability^{93,119,120}.

5.4.5 CTLA4-Targeted Therapy

CTLA-4 is regarded as the primary immune checkpoint inhibitor because it halts T cells that could potentially assault the body's tissues when they are still naive and in the early phases of activation. This process usually takes place in the lymph nodes^{121,122}. CTLA-4 is a receptor that belongs to the B7 family and has a 30% similarity with CD28. However, unlike CD28, CTLA-4 has a stronger binding affinity for both B7-1 and B7-2¹²³. B7-1 (CD80) or B7-2 (CD86)-binding properties of CTLA-4 prevent the activation of antigen-presenting cells¹²⁴.

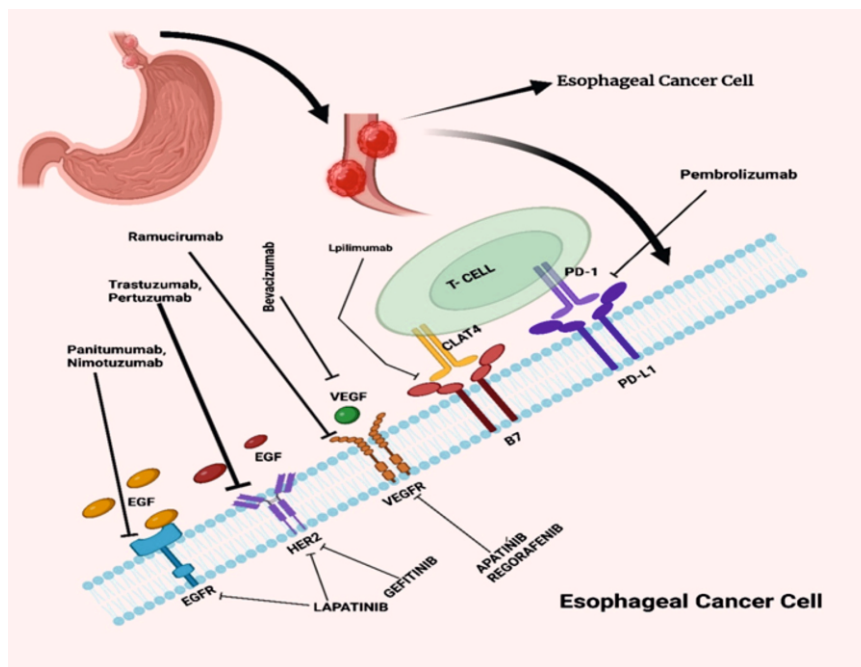


Fig. 4: - EC is a complex disease that requires a multifaceted approach to treatment. Targeting various proteins such as EGF, EGFR, HER2, VEGF, and VEGFR, as well as immune checkpoints like CTLA-4, PD-1, and PD-L1, offers a promising strategy for improving outcomes for patients with this condition. The ongoing research in this area highlights the importance of continued investigation and innovation in cancer therapeutics.

Table 3: Molecular entities registered in a clinical trial for EC

Agent	Description	Entities /phase	Proposed mode of action	Sponsor	References
Drug cisplatin Drug irinotecan HCl	This phase 2 trial studies how well giving cisplatin and irinotecan together with radiation therapy works in treating patients with EC that can be removed by surgery.	NCT00316862 /Phase 2	Radiation therapy uses high-energy X-rays to kill tumor cells. Giving combination chemotherapy with together with radiation therapy before surgery may make the tumor smaller and reduce the amount of normal tissue that needs to be removed	Alliance for clinical trials in Oncology	[125]
Drug Camrelizumab + Radiotherapy Drug Camrelizumab	The purpose of this study is to observe and evaluate the efficacy and safety of carelizumab combined with or without radiotherapy for the treatment of recurrent or metastatic EC that has progressed after chemotherapy.	NCT04512417 /Phase 2	It is a humanized IgG4 Kappa anti-programmed cell death 1 (PD -1) monoclonal antibody used in EC. The blockade of PD-1 binding to its ligand PD-L1 enables the reactivation of cell-mediated immune response against cancer cells.	Zhejiang cancer hospital	[126]
Drug oxaliplatin Drug cisplatin	Phase 2 study of radiochemotherapy for elderly patients with EC with radiotherapy =50Gy, 2Gy /f and chemotherapy with 2 arms cisplatin = cisplatin 75mg/m2 J1J22 or arm oxaliplatin = oxaliplatin 85mg /m2 every 2 weeks	NCT02879227 /Phase 2	Cytotoxicity results from selective inhibition of tumor DNA synthesis by the formation of intra and interstrand cross-links in the DNA molecule.	Centre Hospitalier Universitaire de Besancon	[127]

Table 3 (continued): Molecular entities registered in a clinical trial for EC

Agent	Description	Entities/Phase	Result	sponsor	Reference
Docetaxel Drug 5 FU Radiotherapy Esophagectomy Drug dexamethasone	The goal of this clinical research study is to learn if giving chemotherapy and radiation therapy before surgery for early - stage EC can help to control the disease and if so, for how long.	NCT01217060/Phase 1 Phase 2	This is a single-arm phase 2B trial of chemoradiation followed by surgery for patients with early -stage T1b EC	M.D Anderson cancer center	[128]
Pembrolizumab	In this study participants with advanced/metastatic adenocarcinoma of the esophagus, SCC of the esophagus, or advanced/metastatic Siewert type 1 adenocarcinoma of the esophagogastric junction, who had been previously treated with two standard therapy, will be treated with Pembrolizumab	NCT02559687/Phase 2	Not available	Merck Sharp & Dohme LLC	[129]
Paclitaxel Poliglumex, Cisplatin and radiation	32 patients with esophageal or gastroesophageal junction cancer will receive Radiation:50.4 Gy at 180cGy fraction/day for 28 treatments and Paclitaxel Poliglumex (PPX) and Cisplatin weekly times 6 followed by surgery	NCT00522795/Phase 2	Twelve of 37 patients (32%) had pathologic complete responses. The 12 patients with pathologic CR all had adenocarcinoma	Brown University	[130]

CONCLUSION

This review summarizes current findings on EC targeted therapy medicine, with a particular emphasis on those that are most likely to be approved for use in clinical trials. The TNM systems staging is essential for directing care and influencing overall survival. Which involves the treatment strategies according to different stages of EC. The mainstay of treatment is multimodality therapy, which includes surgery, radiation, chemotherapy, endoscopic treatment and targeted therapies. Despite substantial advancements in EC management over the past few decades, surgery is still a vital component of care. Robotic surgeries is the minimum strategy that surgeons are currently researching to lower morbidity and mortality in high risk surgeries. The survival and prognosis of patients with advanced EC have been demonstrated to be improved by PD-L1, VEGFR, and HER-2 inhibitors.

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