



Review Article

A Review Of The Pathophysiology, Staging, Therapeutic Options, And Epidemiology Of Esophageal Cancer

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ABSTRACT

A malignant tumor called esophageal cancer grows in the inner layers of the esophageal mucosa, or lining. It ranks eighth among the most prevalent cancer globally and is distinguished by significant regional, ethnic, and gender variations. Although they have different histopathologic and epidemiologic characteristics, the two primary forms of esophageal cancer squamous cell carcinoma and adenocarcinoma share a dismal prognosis. This page gives a summary of esophageal cancer, including its worldwide incidence, protective factors and known and suspected risk factors; illness signs and symptoms; typical diagnostic and treatment processes; and public health implications.

INTRODUCTION

Healthy cells can undergo uncontrollable growth and alteration to become a tumor, which is the first sign of cancer. A tumor may be benign or malignant. Because a tumor that has cancer is malignant, it has the potential to develop and disperse to other bodily parts. When a tumor is benign, it is able to expand but not spread. The cells lining the esophagus are where esophageal cancer. In particular, esophageal cancer begins in the lining of the esophageal wall and spreads outward. Should it breach the esophageal wall, it has the potential to reach the chest's blood vessels,

adjacent organs, and lymph nodes tiny, bean-shaped organs that aid in the battle against infection. Additionally, esophageal cancer has the potential to spread to the stomach, liver, lungs, and other body organs. Cancer of the esophagus is the sixth most common cause of cancer-related mortality worldwide because of its high malignant potential and poor prognosis. One of the most deadly cancers in the world is esophageal cancer (EC), also known as ESCC, and adenocarcinoma of the esophagus (EAC), which includes squamous cell carcinoma of the esophagus.¹The prognosis for esophageal cancer

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(EC), an aggressive cancer, is not good and its incidence is rising. Histologically speaking. There are two primary groups of EC: carcinoma of the squamous cell (ESCC) and adenocarcinoma (EAC). Esophageal cancer (EC) ranks sixth globally in terms of cancer-related mortality (436,000 deaths) and is the most frequent reason for cancer globally (473,000 cases). In contrast to numerous other malignancies, the pathophysiology of EC is comparatively little understood, and when it is detected, it typically exhibits exceptionally aggressive clinical signs. As a result, Based on a 5-year survival ratio of 15-20%, EC is considered the sixth most common cause of cancer-related death.

The two primary EC histological subtypes, Different clinical and epidemiological features distinguish esophageal squamous cell carcinoma (ESCC) from esophageal adenocarcinoma (EAC).. With 80% of EC occurrences worldwide, ESCC is the most common subtype of EC and can anatomically form anywhere along the esophagus. However, The most common kind among white populations in developed nations is EAC (20%), which typically develops proximal esophageal tube. The incidence of EAC has been confirmed to be significantly and continuously rising in western nations, while the incidence of ESCC is decreasing globally.

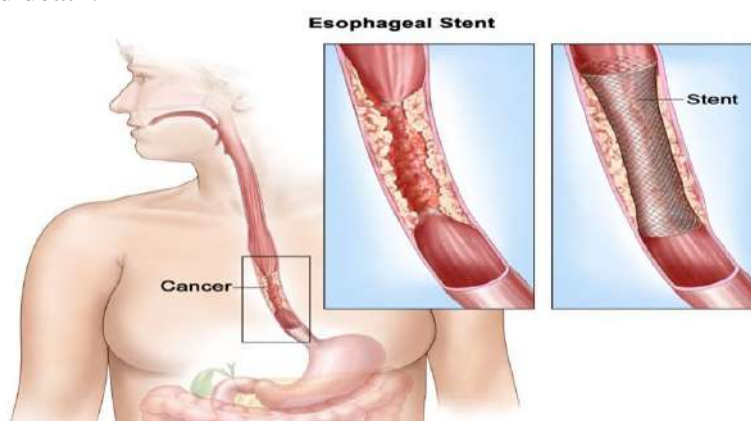


Figure 1: Esophageal cancer

- **Esophageal cancer types**
- Esophageal cancer comes in two primary forms:
 - **Squamous cell carcinoma**

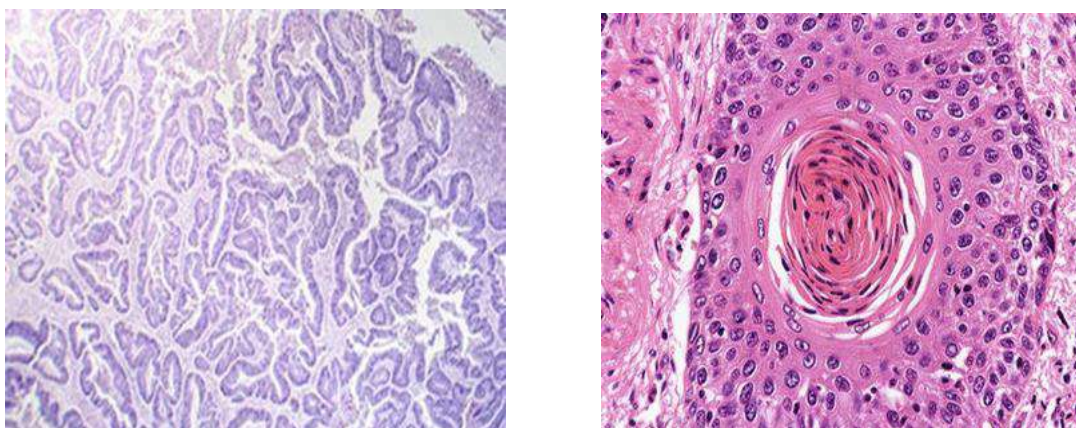


Figure 2: Squamous cell carcinoma

The thin, flat cells called squamous cells lining the throat are affected by this kind of cancer of the esophagus. Any portion of the esophagus can develop squamous cell carcinoma, but the upper to middle section which is found in the neck and upper two thirds of the chest is where cancer most frequently manifests. Approximately 50% of

esophageal cancer diagnosis in the US is now of the squamous cell, however being the most common kind in the past due to recent advancements in therapy. Still, it remains the most prevalent kind of esophageal cancer globally.

- **Adenocarcinoma**

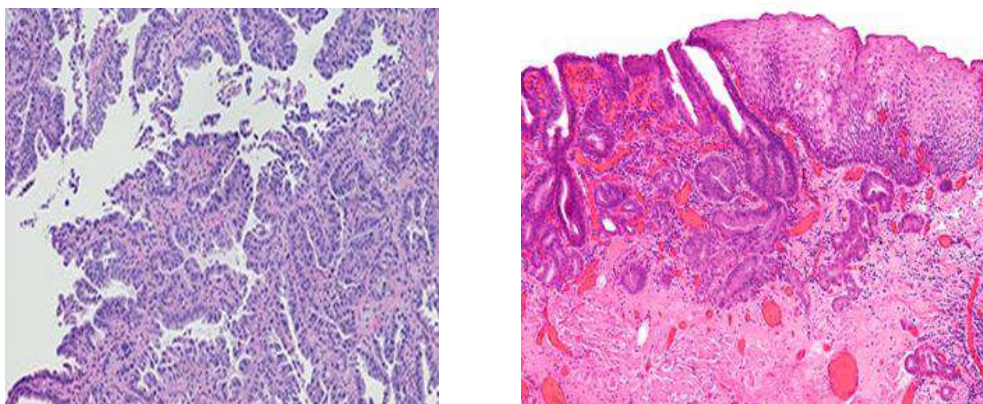


Figure 3: Adenocarcinoma Cell

The most prevalent kind of gastric cancer in the US is called adenocarcinoma. Mucus-producing gland cells need to be swapped out a portion of the squamous cells capable of normally line the esophagus for esophageal adenocarcinoma to occur. Barrett's esophagus, a consequence of gastrointestinal reflux disease, is connected to a frequent transition in which the cells that border the esophagus mutate to resemble the cells lining the intestine. As such, a higher chance of developing esophageal cancer could be linked to Barrett's esophagus. But it doesn't always mean that cancer will manifest.³

Epidemiology

SCC is the most common histological kind of esophageal cancer globally, although adenocarcinoma of the esophagus is in more prevalent in a few developed nations such as Australia, Finland, France, United States and the United Kingdom. In 2020 there were an approximate 0.6 million new instances of gastric cancer and 0.54 million deaths occurred due to this disease based on GLOBOCAN 2020. The

techniques employed to estimate the global 2020 cancer death and incidence figure are founded on the most recent data supplied by the population-based. XI cancer registries are maintained through the Worldwide Agency for Cancer Research (IARC). It is well recognized that there are differences in esophageal cancer. The most prevalent kind of histology worldwide for esophageal cancer is esophageal SCC. SCC and AC are the other major histological kinds. These two kinds of histopathology have different incidences depending on factors like race, lifestyle, and geography.⁴

RISK FACTORS

Race and gender: Adenocarcinoma is more prevalent in white men than in black people, and for histological types, squamous cell carcinoma is the most prevalent. In both groups ($P < 0.001$). In most nations, men are more likely than women to get gastric squamous cell cancer, and in the US, black men are more likely than white men to develop the disease.

Smoking: One of the main Esophageal squamous carcinoma risk factors development is smoking. The risk of this disease among smokers is five times more than in non-smokers.

Alcohol: There is little doubt that alcohol use raises the possibility of squamous carcinoma. Relative risk (RR) rises as alcohol use rises, with weekly volume-related variations in RR ranging from 1.8 to 7.4. Around the world, specific drink types have been connected to "hot spots" of gastric squamous cell carcinoma.

Genetics: The onset of gastric carcinoma of the squamous cellis firmly linked to certain disorders with a hereditary foundation, such as the autosomal dominant disease tylosis. There have also been reports of familial aggregation in populations with high rates of gastric cancer, like those in China's north.⁵

Esophageal adenocarcinoma risk factors

Gender and race: Esophageal adenocarcinoma frequency in the US is 5-fold higher compared to Blacks in Whites, and 8-fold higher in males than in women.

Obesity: A significant and continuous risk factor for the emergence of gastric cancer is obesity. In wealthy nations, it has turned into a severe public health issue. According to estimates, 41% of Americans will be overweight (body mass index > 30) and 75% of overweight adults (BMI > 25) by 2015.

Alcohol, tobacco, and nutritional deficit: With an OR of 2.7 (95%CI: 1.64-4.45) smoking tobacco is a recognized risk factor. Compared to non-smokers, however alcohol is not linked to the existence of adenocarcinoma.

Drugs: PPIs, or proton pump inhibitors, statins, and non-steroidal anti-inflammatory medications (NSAIDs) were found to reduce the rate of BE development patients' cancer to adenocarcinoma in observational studies including a large patient population.⁶

Esophageal Cancer: Symptoms and Signs

The following indications or symptoms may be present in people with esophageal cancer. Changes in your body that you may feel are called symptoms. Alternatively, a sign or symptom could be caused by a medical condition other than cancer. Pain and difficulty swallowing, especially after consuming raw veggies, bread, or meat. The tumor may obstruct the stomach's entrance as it expands. It could be unpleasant to swallow even liquids.

- A burning or pressure in the chest
- Indigestion or heartburn
- Vomiting
- Frequently suffocating on food
- Unexplained weight loss
- Coughing or hoarseness
- Soreness in the throat or beneath the breastbone

Stage groups for esophageal cancer:

Adenocarcinoma and Squamous Cell Carcinoma, the two most prevalent types of gastric cancer, have different staging methods.

Treating Esophagus Cancer :1. Surgery for Esophageal Cancer: Surgery may be done to try to remove some cancer and normal surrounding tissue from some earlier stage malignancies.

Esophagectomy: An esophagectomy is the partial or complete excision of the esophagus during surgery. If the cancer hasn't already spread too far, it may be cured by removing the esophagus and any nearby lymph nodes.

2. Radiation Therapy for Esophageal Cancer:

High-energy rays, like x-rays, or particles are used in radiation treatment to kill cancer cells. It is commonly used in conjunction with other treatments including chemotherapy and surgery to treat esophageal cancer. When chemotherapy is added to radiation therapy, some esophageal cancers may respond better to the treatment. Combining these two therapies is known as "chemoradiation."



Far, it hits the tumor with minimal impact on the normal tissues that are close by. Generally speaking, this results in less negative effects than with radiation from external beams. A short while later, the radioactive source is eliminated.⁷

Chemotherapy for Esophageal Cancer

Anti-cancer medications known as chemotherapy (chemo) can be either injection or orally (injected into a vein). The drugs enter the bloodstream and travel to most of the body's cancer cells.

Side effects of chemotherapy

Chemotherapy medications may have negative effects. Their duration and the kind and dosage of medications administered determine this. Among the most typical chemo adverse effects are:

- Nausea and vomiting
- Loss of appetite
- Hair loss
- Mouth sores
- Either constipation or diarrhea

Targeted Drug Therapy for Esophageal Cancer

Standard chemotherapy medications do not function in the same way as targeted drugs.

Drugs that target HER2:

Overexpression of the HER2 protein on the surface of some esophageal tumors can promote the growth of cancer cells. The overabundance of

copies of the HER2 gene results in an excess of this protein. HER2-positive cancers have elevated HER2 expression. Treatment for HER2-positive tumors frequently involves the use of medications that target the HER2 protein.

1. Trastuzumab (Herceptin others)

Certain HER2-positive tumors of the gastroesophageal (GE) junction the area where the esophagus and stomach meet may benefit from its use. Monoclonal antibody that targets HER2 is called trastuzumab.

2. Fam trastuzumab deruxtecan This is a monoclonal antibody-drug conjugate (ADC), which is connected to a chemotherapeutic medication.

3. Entrectinib and larotrectinib

Certain tumors have genes that combine in their cells. One of these genes, NTRK, can fuse with another gene to cause aberrant cell proliferation known as TRK inhibitors, these medications target this aberrant gene fusion and include entrectinib (Rozlytrek) and larotrectinib (Vitrakvi).

Side effects of entrectinib and larotrectinib

Fatigue, nausea, vomiting, dizziness, cough, diarrhea, and constipation are the most frequent adverse effects. Liver issues and disorientation are two more severe but uncommon side effects.

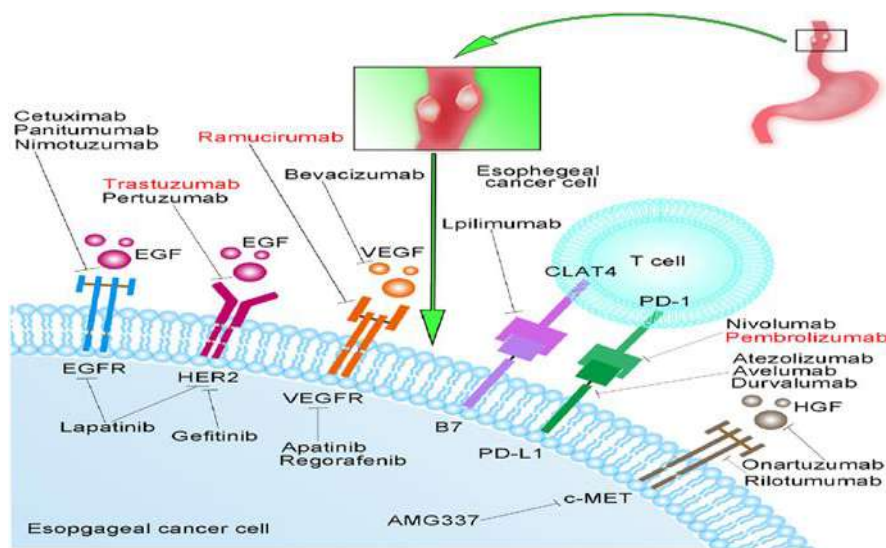


Figure 4: Advances in targeted therapy for esophageal cancer

Immunotherapy for Esophageal Cancer

The use of medications to enhance an individual's immune system's capacity to identify and eliminate cancer cells is known as immunotherapy. It is effective in treating certain patients with esophageal cancer. Figure 4: Advances in targeted therapy for esophageal cancer

PD-1 Inhibitors: 1. Pembrolizumab (Keytruda) and Nivolumab (Opdivo)

are medications that target the protein on T cells (a subset of immune system cells) called PD-1. Normally, the PD-1 protein aids in preventing T cells from attacking other bodily cells. These medications strengthen the immune system's defense against cancer cells by inhibiting PD-1

2. **Pembrolizumab** can be used to treat some advanced esophageal or gastroesophageal junction (GEJ) cancers, usually in cases where other treatments like surgery or chemoradiation (chemotherapy combined with radiation therapy) are not effective. Depending on the circumstances, pembrolizumab may be used alone or in combination with chemotherapy (and maybe the targeted medication trastuzumab, in the event that the malignancy tests positive for HER2).

3. **Nivolumab** can be used in different situations:

- If postoperative laboratory testing reveal residual cancer, it may be utilized in patients with esophageal or gastroesophageal junction (GEJ) cancer who received chemotherapy and radiation therapy (chemoradiation) prior to surgery.
- In patients with advanced esophageal squamous cell cancer, it can be used on its own, usually following a trial of chemotherapy.

CTLA-4 inhibitor:

1. **Ipilimumab (Yervoy)** is an alternative drug that likewise boosts the immune response. It suppresses CTLA-4 an extra T cell protein that frequently helps to regulate them.

If you have advanced esophageal squamous cell carcinoma that is incurable or has spread to other parts of your body, you can use it as your first line of treatment in addition to nivolumab⁸

Photodynamic therapy

Therapy with photodynamics (PDT) is an uncommon but effective treatment for dysplasia, Barrett's esophagus, and some very early stage esophageal cancers. Its application may also be necessary with the purpose of treating large tumors that are blocking the esophagus. PDT in this instance seeks to minimize the cancer to the point where it will no longer impair the patient's capacity to swallow⁹

Argon plasma coagulation This technique uses argon gas and sends a high-voltage spark through the tip of an endoscope, much to laser ablation. Once The gas reaches because of the spark. extraordinarily high temperatures, it can be guided towards the tumor. This technique is meant to assist those who struggle with swallowing by clearing obstructions in their esophagus.

Electrocoagulation (electrofulguration) Using an endoscope a probe is inserted into the esophagus during this surgery and an electric current is utilized to destroy the tumor by burning it. In some cases, this surgery might be helpful to relieve esophageal blockage.

Novel Nanoplatfrom Found Effective Against Esophageal Cancer:

Nanotechnology based Cancer Treatments:

Due to their many unique properties and nanoscale dimensions (100–200 nm) nanoparticles are frequently employed in biological studies. Carbon nanodots are one type of carbon nanoparticle that is utilized in fluorescence sensing, bioimaging, and medication delivery. Tumor-targeted drug delivery systems need to be created in order to allow for tumor-specific treatment without having an adverse effect on normal cells. Medications are frequently



altered to recognize particular receptors generated by tumor cells, allowing for their identification. An overabundance of the epidermal growth factor receptor (EGFR) has been observed in a variety of cancer types, including cancer of the stomach. Patients with esophageal cancer have significantly higher mucosal expression of the EGFR protein than do healthy individuals. Therefore, the administration of anti-tumor medicines has targeted this receptor as its major target.¹⁰

A Novel Theranostic Nanoplatform for Esophageal Cancer Treatment:

Recently, scientists developed GCDs-Ce6/Pt-EGF, Drug carriers were created using green fluorescent carbon dots (GCDs), which have excellent optical properties, modifiability, and low toxicity. To achieve tumor-specific targeting, epidermal growth factor (EGF) was coupled to the nano-assembly. Reactive oxygen species (ROS) that promote apoptosis are produced by chlorin e6 (Ce6) when exposed to laser radiation. An integrated theranostic nanoplatform for the management of esophageal cancer. Carbon dots with green fluorescence were used in this nanoplatform. For six hours, p-aminobenzamide and p-aminosalicylic acid were hydrothermally mixed in a molar ratio of 1:1 at 200°C to create GCDs. Eleven Esophageal Cancer Screening Screening aims to detect cancer before symptoms manifest. This may aid in the early detection of cancer. Early detection of cancer or abnormal tissue may lead to simpler treatment. The disease may have started to spread by the time symptoms show up.

There isn't a regular or accepted screening procedure for esophageal cancer.

Despite the lack of a set or regular screening procedures for esophageal cancer, the following tests are being investigated or used as screening tools:

Esophagoscopy

esophageal endoscopy that involves peering within the stomach to look for irregularities. One inserts an esophagoscope through the nose or mouth into the esophagus and past the throat. A small, tube-shaped device with a light and a viewing lens is called an esophagoscope. Additionally, a device for removing tissue samples might be present. These samples are subsequently examined under a microscope to look for indications of cancer.¹²

CONCLUSION:

Cancer of the esophagus is a dangerous type of cancer that has a serious impact on how long people live and their chances of getting better. It is becoming a big worry for people's health and it is expected to happen more in the the following ten years. Esophageal The most common places where cancer is detected a type called SCC especially in developing countries. As more people in developed countries have acid reflux and are obese, the number of instances of cancer of the stomach has gone up a lot in the last 40 years. Esophageal cancer is put into different stages based on the TNM framework. Putting on plays a very important role in deciding how to treat cancer at each stage, and it greatly affects how long someone will live. Common ways to take pictures inside the body to see how a disease is spreading include CT scans, EUS, PET scans, etc. Present ways to treat cancer include using a combination of chemotherapy, radiation, and surgery. These are the most prevalent treatments used right now. Scientists are studying substances in the body that can show if someone has esophageal cancer. They think this could help find the cancer sooner and see how well treatment is working.

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