"CORRELATION OF HUMAN PAPILLOMA VIRUS AND EPSTEIN BARR VIRUS IN ESOPHAGEAL AND GASTRIC CARCINOMA IN A TERTIARY CARE CENTER"

By

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DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, KOLAR, KARNATAKA

In partial fulfilment of the requirements for the degree of

M.S. GENERAL SURGERY

Under the Guidance of

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ABSTRACT

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LIST OF ABBREVIATIONS

EBV	Epstien Barr Virus
HPV	Human Papilloma Virus
GC	Gastric Carcinoma
EC	Esophageal Carcinoma
SCC	Squamous Cell Carcinoma
AC	Adenocarcinoma
ESCC	Esophageal Squamous Cell Carcinoma
EAC	Esophageal Adenocarcinoma
GEJ	Gastroesophageal Junction
GERD	Gastroesophageal Reflux Disease
HER2	Human Epidermal Growth Factor Receptor 2
PCR	Polymerase Chain Reaction
CT	Computed Tomography
PET CT	Positron Emission Tomography CT
EUS	Esophageal Ultrasound
TNM	Tumour, Node, Metastasis
ER	Endoscopic Resection
CCRT	Concurrent Chemoradiotherapy
NACT	Neoadjuvent Chemotherapy
RT	Radiotherapy
GJ	Gastro-Jejunostomy
JJ	Jejuno-Jejunosotmy
TTE	Transthoracic Esophagectomy

ABSTRACT

BACKGROUND: Gastric and oesophageal cancers have similar high disease-related fatalities, with over 1.3 million deaths from them in a single year. Both sites exhibit distinct geographical and temporal trends in incidence, but also share several risk factors and epidemiological aspects due to their close anatomic proximity. There are very few known studies conducted in our subcontinent till date, hence we conducted this study to find the correlation between HPV & EBV in Esophageal and Gastric Carcinoma in South India.

METHODOLOGY: 32 patients with early or advance carcinoma of esophagus and stomach were included in the study. Those with Sewart Class II carcinoma were excluded. PCR test was run on the tissue samples for both the viruses i. e. EBV & HPV. The SPSS software for Windows, version 17.0, was used to conduct the statistical analysis (SPSS, Chicago, Illinois). Categorical data were shown as absolute numbers and percentage, whereas continuous variables were shown as mean ± SD. Prior to statistical analysis, the normality of the data was examined.

RESULTS: Out of 32 cases, 16 (50%) were and 16 (50%) were stomach carcinoma. Among the 16 patients with esophagus carcinoma, squamous cell carcinoma was the most common type (68. 8%), followed by adenocarcinoma (25. 0%), and poorly differentiated carcinoma (6. 3%). Adenocarcinoma accounted for 14 cases, representing 6. 3% of the total, while poorly differentiated cases total 2, comprising 75. 0%. Moderately and poorly differentiated cases are equally prevalent, each comprising 37. 5% of the total cases. Out of the total esophagus cases HPV positive was not observed in any case of esophagus carcinoma and HPV positive was found in 2(2. 5%) in gastric cases. EBV was positive in 5 (31. 2%) esophagus and 6 (37. 5%)

gastric carcinoma cases. There was a statistically significant difference between the distributions of lymph node involvement in the esophagus and stomach.

CONCLUSION: In the present study, we observed the presence of EBV virus infection in both Oesophageal and gastric cancers, while HPV was not prevalent in Oesophageal, only a minority of the patients with gastric cancers were positive for EBV.

It also showed an association between the number of nodes retrieved for virus-positive cases compared to those that were negative for the virus; hence, going forward, the number of nodes retrieved can be increased for better clearance of the viral burden reducing the chances of spread secondary to the viral load.

KEYWORDS: Esophageal Carcinoma, Gastric Carcinoma, Epstein Barr Virus (EBV), Human Papilloma Virus (HPV), Lymph Node, Margins Positive, Staging

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INTRODUCTION

INTRODUCTION

Cancers of the stomach and esophagus are both prevalent and fatal. Patients usually present after the disease has progressed, which makes survival low. Globally, gastric cancer (GC) and oesophageal cancer are among the most frequently diagnosed cancers, with an expected 1.5 million new cases in 2018. [1,2] Both have a high disease-related mortality rate, with about 1.3 million deaths occurring in a single year. [1-3] Both sites exhibit distinct geographical and temporal trends in incidence, but also share several risk factors and epidemiological aspects due to their close anatomic proximity. It has been discovered that variations in the burden of gastric cancer (GC) and oesophageal cancer (OC) among populations can be partially explained by variations in the distribution of tumor subtypes. [4,5] To maximize therapy, extensive research must be conducted in the future.

Infectious pathogens are thought to be the cause of 15% to 20% of all human malignancies worldwide. [6,7] Twelve percent of these cancers are caused by seven viruses: the Epstein-Barr virus (EBV), hepatitis B virus, hepatitis C virus, T-cell lymphotropic virus, hepatitis C virus, Kaposi's sarcoma virus (KHSV)/human herpesvirus 8 (HHV-8), and Merkel cell polyomavirus. Depending on the viral pathogen, viruses can be involved in the carcinogenesis pathway at different stages. To cause neoplasia, viruses probably need co-factors such as smoking, using contraceptives, nutrition, co-infection with herpesvirus and chlamydia, human immunodeficiency virus (HIV) in cervical cancer, alcohol, and aflatoxin in hepatocellular carcinoma. [7–10] Viral DNA integration into the host genome can initiate tumors by upregulating the expression of cellular oncogenes, causing DNA damage and chromosomal instability. Viral proteins can also cause dysregulation of cellular processes, such as proliferation, apoptosis, and replicative immortality. Certain viruses, such as HBV and HCV, induce hepatocellular cancer indirectly by causing chronic inflammation over many years,

which is exacerbated by alcohol and aflatoxin co-factors.[11] The relationship between viruses and the immune system, and the ensuing development of immune evasion techniques, is another essential process in the carcinogenesis of viruses. These include of creating escape mutants, interfering with the function of interferons, downregulating the major histocompatibility complex (MHC), and molecular mimicry.[7]

Oesophageal and stomach cancer have been linked to a number of risk factors, including carcinogenic microorganisms. These bacteria and viruses include Helicobacter pylori (HP) [non-cardia stomach cancer], Epstein-Barr virus (EBV) [proximal stomach cancer], and human papillomavirus (HPV) [oesophageal cancer]. [12–14]

HPV prevalence in patients with OC ranging from 13% to 35%.[15] 8. 4% of stomach malignancies (mostly adenocarcinomas) are linked to EBV. The likelihood of EBV positivity was significantly higher in proximal cancers (cardia and corpus) (13.6%) than in antral tumors (5.2%).[16]

There are very few known studies conducted in our Subcontinent till date, hence we conducted this study to find the correlation between HPV & EBV in Esophageal and Gastric Carcinoma in South India.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

1. Study the number of positive cases of HPV and EBV in Esophageal Carcinoma in R. L. Jalappa Hospital, Tamaka.
2. Study the number of positive cases of HPV and EBV in Gastric Carcinoma in R. L. Jalappa Hospital, Tamaka.

REVIEW OF LITERATURE

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ESOPHAGEAL CANCER

Even with treatment, esophageal cancer is a terrible disease with a very poor chance of survival. With an approximate annual incidence of 16,940 cases, esophageal malignancies rank fifth among gastrointestinal cancers in the United States and sixth globally.

Most esophageal cancers can be classified as either adenocarcinoma (ADCA) or squamous cell carcinoma (SCC) based on histology. The incidence of these carcinomas has been rising (more than 60%) and falling (less than 30%) in the US during the last three decades. Due to Barrett's esophagus, the incidence of adenocarcinoma of the distal esophagus and gastroesophageal junction (GEJ) continues to rise quickly when categorized by anatomical location. [17-19]

Etiology:

A diet deficient in fruits and vegetables, combined with a history of smoking and alcohol usage, is responsible for over 90% of cases of esophageal squamous cell carcinoma. Risk factors for esophageal squamous cell carcinoma in underdeveloped nations are less clear, however they could include eating a diet low in fruits and vegetables, drinking hot beverages, and having poor nutritional status. Squamous cell carcinomas of the upper esophagus have been linked to higher incidences of human papillomavirus (HPV) infection. Achalasia, caustic strictures, gastrectomy, and atrophic gastritis are a few structural conditions that are linked to a higher risk of esophageal squamous cell carcinoma. Synchronous or metachronous squamous cell carcinoma of the esophagus may be associated with a patient's past or present aerodigestive tract cancer. Early diagnosis of esophageal squamous cell carcinoma is possible in patients with Bloom syndrome, an uncommon autosomal recessive syndrome linked to lymphomas,

leukaemia, and Wilms tumor (also known as chromosomal breakage syndrome). Fanconi anaemia is an autosomal recessive condition that increases the risk of squamous cell carcinoma in addition to congenital abnormalities, pancytopenia, and hematologic malignancies.

Majority of esophageal adenocarcinomas in the US are caused by Barrett metaplasia, of which smoking, a high body mass index, GERD, and a diet deficient in fruits and vegetables are associated with 80% of cases. There is no correlation between alcohol consumption and adenocarcinoma. Epidermal growth factor polymorphisms and other diseases that enhance esophageal acid exposure, such as scleroderma, Zollinger-Ellison syndrome, lower esophageal sphincter relaxing medications, and procedures, have been linked to Barrett esophageal metaplasia. Patients with esophageal/GEJ adenocarcinoma should be suspected of having it, especially if they are white men over 40 who also have GERD. Antioxidants, fruits and vegetables, folate, vitamin C, proton-pump inhibitors, NSAIDs, and a high-fibre diet can all help prevent Barrett esophagus and, consequently, esophageal adenocarcinoma from developing and progressing. However, none of these interventions have been proven to be effective in preventing the disease itself.[20,21]

Epidemiology:

The sixth most frequent cancer in the world is oesophageal carcinoma. Squamous cell cancers account for 90% of all instances in the highest-risk region, known as the "esophageal cancer belt," which includes parts of northern Iran, southern Russia, central Asian nations, and northern China. Esophageal cancer ranks as the fourth most common cause of cancer in this risk area. On the other hand, the United States is regarded as a low-risk region, with a steady decline in squamous cell carcinoma because of long-term reductions in alcohol and tobacco use, and an increase in the incidence of esophageal adenocarcinoma primarily due to an increase in obesity and GERD. Male Caucasian persons are predominantly affected with

adenocarcinoma. On the other hand, Asians and Blacks have the greatest incidence rates of esophageal squamous cell carcinoma.[22]

Pathophysiology

Small polypoid excrescences, denuded epithelium, and plaques that are typically found in the midsection of the esophagus are the precursors of esophageal squamous cell carcinoma. Although a third of patients will experience distant metastases to the liver, lung, and bone, including the invasion of malignant cells into the bone marrow, the disease spreads via the lymphatic system to local lymph nodes.

About 60% of distal esophageal adenocarcinomas and, more frequently, GEJ cases are caused by Barrett esophageal metaplastic epithelium. Patients with Barrett's esophagus usually receive surveillance using upper endoscopy and biopsy to look for dysplasia in the tissue. In individuals without dysplasia, the incidence rate of adenocarcinoma is 1. 0 instances per 1000 person-years; however, an incidence rate of 5. 1 case per 1000 person-years is linked to the identification of low-grade dysplasia on the index endoscopy. Esophageal adenocarcinoma had an annual risk of 0. 12% (95% CI: 0. 09, 0. 15). A strong course of treatment is necessary for high-grade dysplasia, which may involve surgical resection. Early metastases happen in lymph nodes nearby or in the same area.

Evaluation of the human epidermal growth factor receptor 2 (HER2) gene and protein expression has been connected to lymph node metastasis and tumor invasion, which are linked to decreased prognosis. Compared to squamous cell carcinoma (13%), adenocarcinoma (30%) exhibits higher levels of HER2 overexpression. For all metastatic adenocarcinomas, HER2 is advised. This should be confirmed initially by immunohistochemistry score (negative for 0 or 1+ and positive for 3+, with reflex FISH for 2+). [23,24]

History and Physical:

Progression of solid food dysphagia due to locally established cancer-causing obstruction and dysphagia to liquids occur in advanced stages of both esophageal adenocarcinoma and squamous cell carcinoma. Dysphagia can result in cachexia and significant weight loss, which may indicate an advanced illness that leaves many patients severely disabled at the time of diagnosis. It's possible that mild, nonspecific sensations like burning or retrosternal discomfort came on first. As part of overt or covert gastrointestinal bleeding, symptoms such as hematemesis, melena, and anaemia may be present at the time of initial diagnosis. Aspiration pneumonia is uncommon; however, regurgitation is another possibility. Clinical manifestations of tracheobronchial wall invasion resulting in fistulas include post-obstructive pneumonia, coughing, and paralysis of the larynx.

Evaluation:

A clinical examination that concentrates on the lymph nodes in the axillary and supraclavicular region is essential. Barium investigations should be carried out on patients who exhibit clinical suspicion, but to confirm the diagnosis, upper GI endoscopy combined with minimally invasive biopsy is necessary. It is recommended that multiple biopsies be performed to collect appropriate histological material with a greater accuracy of diagnosis (93% accuracy for one biopsy, 95% accuracy for four biopsies, and 98% accuracy for seven biopsies). Lugol's iodine staining in vivo is not well-established. [25–30] The early lesion may be inconspicuous, thus in order to help diagnosis, normal squamous epithelium containing glycogen should be stained differently from malignant squamous glycogen-deprived cells using Lugol's iodine tissue staining. Advance lesions are circumferential, ulcerated, penetrate the submucosa, and spread cephalad.

It is recommended to perform computed tomography (CT) scans of the abdomen and thorax to assess the size of the initial tumor and look for possible celiac lymphadenopathy and liver metastases. Nevertheless, CT can be unreliable in differentiating tumor depth, has low sensitivity to lymph nodes, and can sometimes miss tiny metastases, especially in the peritoneum.

With up to 90% accuracy in determining the depth of the tumor and the involvement of the locoregional and mediastinal lymph nodes, endoscopic ultrasonography (EUS) has emerged as the gold standard of therapy for locoregional staging. Furthermore, EUS permits a tiny needle aspiration biopsy of lymph nodes that are suspicious (greater than 1 cm), which is essential for determining the proper staging. One drawback of EUS is that it is unable to detect transverse tumor stenosis, which is a clinical condition that affects one-third of instances and can lead to an underestimated tumor. While EUS lacks the sensitivity to evaluate the full response, it can be utilized following neoadjuvant therapy to restage local disease prior to surgery.

Positron emission tomography CT (PET/CT) has been incorporated into the standard pretreatment diagnostic workup to assess distant metastases. While squamous cell carcinoma typically metastasizes intrathoracic, adenocarcinoma frequently does so to intrabdominal locations. When it is not necessary, as it is in up to 20% of patients, PET enables the identification of hidden locations of distant metastatic spread and avoids the patient the morbidity of an intensive local-regional therapy approach. If metastatic illness is discovered, PET/CT may be clinically helpful in helping patients who have had induction therapy for their locally advanced disease to be excluded from further surgery. In 8% of cases, this happens.

Although it is still debatable, diagnostic laparoscopy for treatable diseases is not usually advised. The eighth version of TNM staging, which was published in 2017, regrouped esophageal squamous cell carcinoma and adenocarcinoma together after previously providing

separate staging for each. One significant modification is that EGJ cancers will henceforth be staged as esophageal if the tumor's epicentre is less than 2 cm (formerly 5 cm) into the proximal stomach. According to the distance to the anatomic junction, Siewert et al. subclassified EGJ into three categories: type I (less than 1 cm), type II (between 1 and 2 cm), and type III (more than 2 cm), with the latter occurring in more than 66% of instances. Location is not as crucial as lymph node count. Half of the patients will have either locally progressed or metastatic disease at presentation, regardless of the histology.

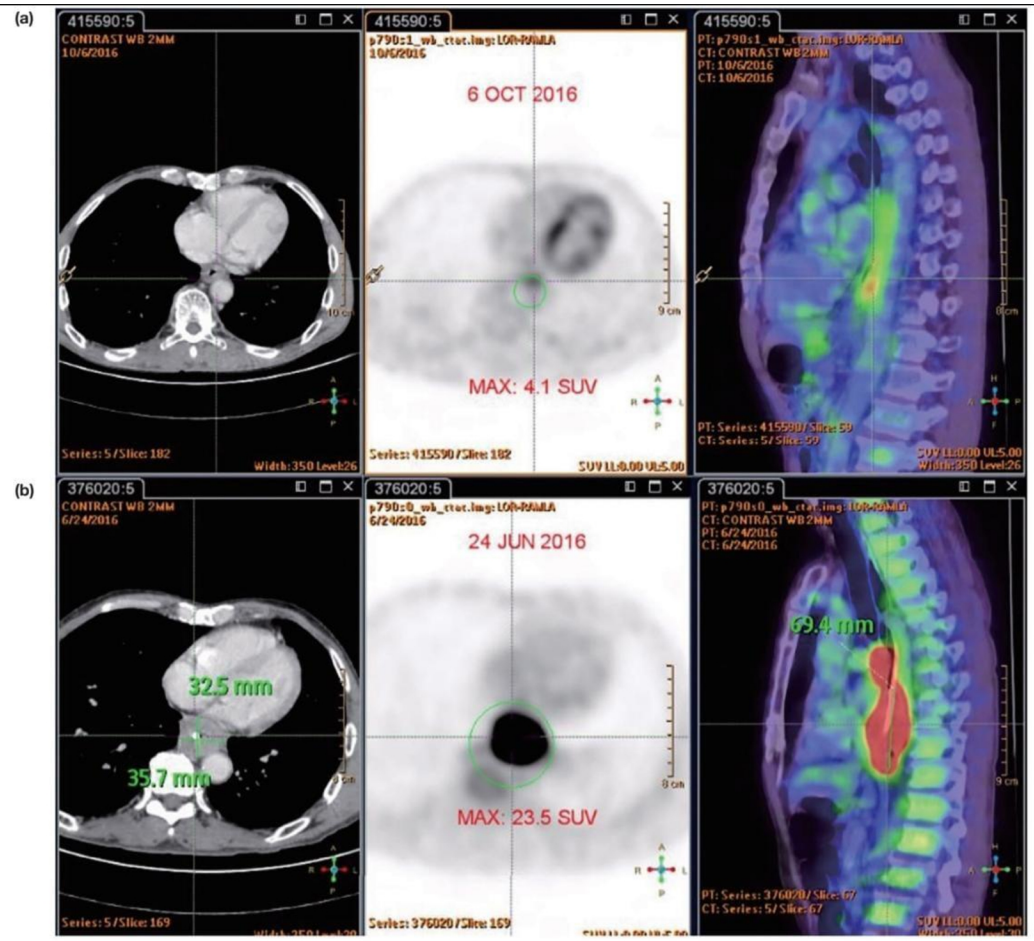


Figure 66.50 Positron emission tomography/computed tomography (CT) scan for staging of oesophageal cancer and assessment of response to neoadjuvant therapy. The patient underwent neoadjuvant chemoradiotherapy. The tumour had high fluorodeoxyglucose uptake (SUV_{max} 23.5) before treatment (b). After chemoradiotherapy the SUV_{max} dropped to 4.1 with a corresponding reduction in size of the cancer seen on CT scan (a).

Figure 1: Easophegeal cancer

Treatment / Management:

Accurate preoperative staging will guide the most appropriate treatment selection. [28,29] The general recommendations are as follows:

- Endoscopic resection for superficial, limited mucosa disease (less than T1a)
- Direct surgical resection with lymphadenectomy for lesions penetrating the submucosa with negative lymph nodes (more than T1b)
- Neoadjuvant chemoradiation of resectable lesions invading muscularis propria with positive lymph nodes (less than T2N1)
- Palliative systemic therapy for those locally advanced unresectable or metastatic disease

Endoscopic Resection

Routine endoscopic surveillance has contributed to an increase in the incidence of superficial esophageal cancer. Lesions limited to the lamina propria or muscularis mucosae may be candidates for endoscopic resection (ER). Patients who have an invasion of submucosa or muscularis mucosae with lymphovascular invasion are not candidates for ER due to an increased risk of lymph node metastasis. ER alternative techniques are endoscopic mucosal resection or endoscopic submucosal dissection, or endoscopic ablation (cryoablation, radiofrequency ablation, and photodynamic therapy). No randomized clinical trial has compared these techniques. ER is reserved for a centre of excellence, interest in pursuing esophagus sparing techniques, high-risk surgical candidates, or elderly patients with multiple comorbid medical conditions. Other esophageal factors that preclude patients from ER are large size lesions (greater than 2 cm), presence and magnitude of Barrett's esophagus, and other esophageal diseases, for example, varices. Patients who undergo ER will require extended and

close follow-up. Patients who are not candidates for ER but are medically fit should be offered esophagectomy; otherwise, chemotherapy and radiation could be an option for patients unfit for surgery.

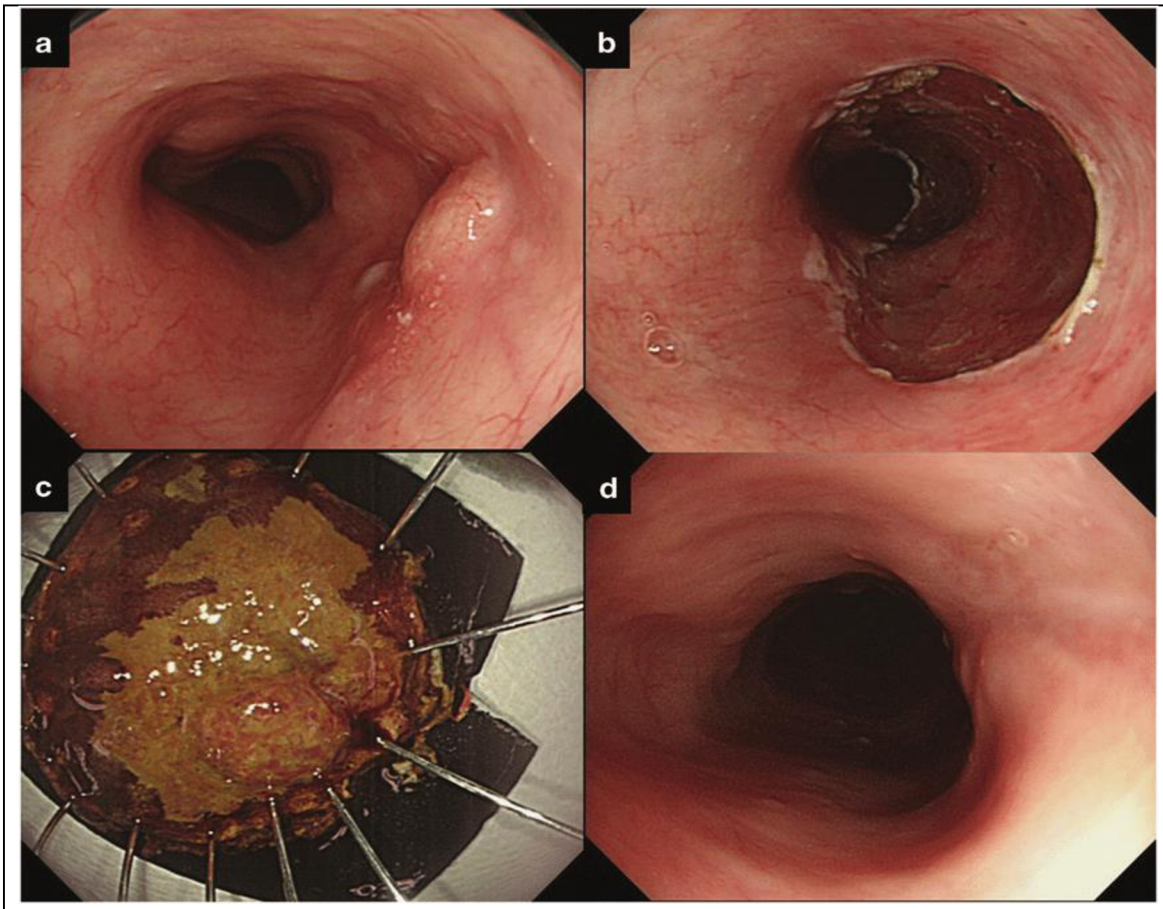


Figure 2: Endoscopic resection for superficial esophageal squamous cell carcinoma (SESCC). (a) SESCC immediately before endoscopic submucosal dissection (ESD). (b) Resection wound immediately after ESD. (c) Resected specimen pinned flat to a hard Styrofoam plate. (d) Follow-up endoscopy performed to check the healing of an ESD induced ulcer before chemoradiotherapy.

Surgical Resection

Localized resectable esophageal cancers comprise approximately 22% of all cases, and those presenting with regional lymph node spread comprise another 30%. The goal of surgical resection is curative. The first-line esophagectomy is offered to T1N0M0 (not endoscopic resection candidate) and selected T2N0M0. Neoadjuvant chemoradiation therapy (CRT) followed by esophagectomy is offered to T2 with positive disease node, T3, and selected T4a disease without metastasis. Relative exclusion criteria for esophagectomy include elderly patients (offered to selected patients) and high-risk patients with comorbid medical conditions. The presence of metastatic disease to other organs or extra-regional lymph nodes is an absolute contraindication to esophagectomy. Surgical procedures are divided accordingly to the anatomical position of esophageal cancer. Cervical esophageal cancer usually requires resection of portions of the larynx, pharynx, thyroid, and proximal esophagus with lower esophagus preservation. Thoracic esophageal cancer will include a total esophagectomy (cervical esophagogastrostomy) with radical two-field lymph node dissection and jejunostomy feeding tube placement. EGJ cancer will involve total esophagectomy and partial or extended gastrectomy. Thoracic cancer resection for the middle to lower esophagus can be divided into three major techniques in the United States: trans-hiatal, transthoracic (Ivor-Lewis), and tri-incisional esophagectomy. Esophagectomy guidelines recommend at least 15 lymph node resections for adequate staging, and this leads to significant reduction in mortality (5-year disease-specific survival; 55% less than 11 nodes were resected, 66% for 11 to 17 nodes resected, and 75% more than 18 nodes resected). A positive circumferential resection margin has higher overall mortality compared to the negative (OR 4.02, 2.25 to 7.20, $p < 0.001$). Reported surgery mortality rates should be less than 5%, and a 5-year survival rate ranges from 5% to 34%. Thoracic, minimally invasive esophagectomy with abdominal laparoscopic intervention offers a surgical recovery advantage with promising better oncologic outcomes over an open thoracotomy and abdominal laparotomy procedure with an experienced surgeon

at a centre of excellence. Patients' nutritional status on esophageal cancer complicated by dysphagia before and after surgery should be monitored and should be palliated with esophageal stents, lasers therapy, endoscopic dilation, and gastric/jejunal feeding tube when necessary and feasible.

Robotic surgery is also a considered option as Robotic systems provide excellent access to the surgical site, including areas that are difficult to reach with traditional methods. This is particularly important in esophageal carcinoma, where tumors may be in challenging anatomical positions.

Lymph Node Dissection: Precise lymph node dissection is critical in staging and treating esophageal carcinoma. Robotic systems enable surgeons to identify and dissect lymph nodes with enhanced precision, potentially leading to more accurate staging and better outcomes.

Tumor Removal with Robotic surgery allows for meticulous removal of the tumor while sparing healthy surrounding tissue, which is crucial for preserving organ function and reducing the risk of complications.

Neoadjuvant Therapy

In the setting of disease localized to the primary site and regional nodes, the use of chemotherapy (CT) or radiation therapy (RT) alone has resulted in a significant improvement in outcome. Radiation therapy, before or after surgery, has been associated with tumor cytoreduction, improved swallowing, and local-regional tumor control, but the combination did not improve survival over surgery alone. Neoadjuvant chemotherapy (without radiation therapy) provides a significant survival benefit over surgery alone; however, it has an uncertain benefit on local control, and results are extrapolated mainly from data. Tri-modality treatment (concomitant chemotherapy and radiation therapy followed by surgery) provides a survival

benefit compared with surgery alone (CROSS trial). The addition of chemotherapy is designed to treat micro-metastases and enhance the local effects of radiation, providing better surgical outcomes (pathological complete response [pCR] and complete resections [R0]).

Adjuvant Therapy

Patients with R0 resection of node-positive or T4 esophageal cancers who have not received neoadjuvant therapy are routinely offered adjuvant chemotherapy or chemoradiation therapy with no randomized trial data to support or refute either approach. Adjuvant chemoradiation therapy for gastric or GEJ has become a standard based on significantly better OS of 36 months compared to observation of 27 months from the SWOG9008/INT 0116 trial (20% GEJ adenocarcinoma).

Systemic Treatment

The treatment goals for metastatic esophageal cancer are symptom palliation, improved quality of life, and prolonged survival. Therapy is guided by symptom burden, performance status, comorbidities, histologic type, tumor-targeted biology, and patient preference. Several chemotherapy agents have demonstrated some activity against esophageal cancer, including fluoropyrimidines (fluorouracil [FU] and capecitabine), platinum agents (cisplatin and oxaliplatin), taxanes (paclitaxel, docetaxel), irinotecan, irinotecan, mitomycin-C, anthracyclines, and, to a lesser extent, methotrexate, vinorelbine, and gemcitabine. Treatment commonly involves a combination of two or three drugs with a response rate as high as 65%, modestly translating to survival of weeks to a few months or, less frequently, as single-agent therapy ranging from 10% to 40%, typically with survival of fewer than 6 months. Palliation therapy may include local interventions (e.g., esophageal stent) and radiation therapy with or without chemotherapy, particularly in scenarios such as dysphagia or bleeding. If available, enrolment in clinical trials is preferred.

In 2021, FDA approved the antibody-drug conjugate fam-trastuzumab deruxtecan for the treatment of advanced HER2-positive gastric or GEJ adenocarcinoma after prior trastuzumab-containing chemotherapy.[30]

Recent Advances In treatment of Esophageal carcinoma:

Targeted Therapies: HER2 Targeting: Trastuzumab, a HER2-targeted monoclonal antibody, has been used in combination with chemotherapy for HER2-positive esophageal cancers, improving outcomes in this subgroup.

EGFR Inhibitors: Drugs like cetuximab are being investigated for their role in targeted therapy for esophageal carcinoma.

GASTRIC CANCER

In the world, gastric cancer ranks third in terms of cancer-related mortality and is the fifth most common type of cancer to be diagnosed. For individuals with stomach cancer, surgical resection combined with a sufficient lymphadenectomy is the only possibly curative therapy strategy. Over the past few decades, the incidence of stomach cancer has declined in the United States, whereas the prevalence of gastroesophageal cancer has concurrently increased. Gastric adenocarcinomas come in two varieties: intestinal (well-differentiated) and diffuse (undifferentiated). Each kind differs in its morphology, etiology, and genetic makeup. For individuals with stomach cancer, surgical resection combined with a sufficient lymphadenectomy is the only possibly curative therapy strategy. Perioperative treatments to increase a patient's chances of survival are supported by available data. Patients with incurable, locally advanced, or metastatic diseases were unfortunately limited to receiving life-extending palliative therapy regimens.[31]

Etiology

Nutritional factors such as high-salt (salt-preserved food), consumption of N-nitroso compounds (dietary source), smoking, low vitamin A and C diet, large consumption of cured or smoked foods, inadequate number of refrigerated foods, and contaminated drinking water are all associated with an increased risk of gastric cancer. Adenocarcinomas of the distal esophagus, proximal stomach, and junction are more common in people with high body mass index (BMI), high calorie intake, gastric reflux, and smoking. The worldwide incidence of Epstein-Barr virus infection is believed to be between 5% and 10%, whereas the associated risk of Helicobacter pylori infection is 46% to 63%. Prior stomach surgery and radiation exposure have also been linked to risk.

High consumption of fruits (RR 0. 90, 95% CI 0. 83-0. 98), vegetables (RR 0. 96, 95% CI 0. 88-1. 06), and Fiber (RR 0. 58, 95% CI 0. 49-0. 67) has been linked to a possible protective advantage against gastric cancer, according to a variety of meta-analyses. The use of aspirin and other non-steroidal anti-inflammatory drugs has been linked to a decreased incidence of gastrointestinal malignancies and cancer of the gastric junction (HR 0. 79 for every year of NSAID usage). There is not enough evidence to support alcohol use as a risk factor; in fact, some studies suggest drinking wine every day may be protective.

Host factors include blood type A, which is specifically linked to the diffuse type and accounts for around 20% more occurrences of gastric cancer than blood types O, B, or AB. The chance of developing intestinal-type stomach cancer is up to six times higher in patients with pernicious anaemia, an autoimmune chronic atrophic gastritis. Hypertrophic gastropathy, benign gastric ulcers, and gastric polyps are risk factors linked to a higher incidence of gastric cancer.

Although 5% to 10% of patients have a familial history of the disease, the majority of stomach cancers are random. Up to 3% to 5% of hereditary familial gastric cancer is caused by three main syndromes: familial intestinal gastric cancer (FIGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and hereditary diffuse gastric cancer (HDGC). Additional inherited cancer syndromes include:

- Hereditary non-polyposis colon cancer, which primarily affects the intestinal type and has a 13% lifetime risk.
- 10% risk for familial adenomatous syndrome (FAP)
- The 29% chance of Peutz Jeghers syndrome (PJS)
- Young people with polyposis syndrome (JPS, 21%)
- Hereditary breast and ovarian cancer syndrome;
- Li-Fraumeni syndrome

- The syndrome known as hamartoma tumor (Cowden's) or phospholipase and tensin homolog (PTEN).

All of these, though, are uncommon reasons of stomach cancer. According to their risk, it is advised to abide by screening recommendations for inherited syndromes linked to stomach cancer.

Epidemiology:

Globally, the prevalence of gastric cancer is dramatically falling. In other places, like China and Japan, the pace has varied, though. The drop in gastric cancer cases may be attributed to the identification and treatment of viral causes as well as dietary and environmental risk factor adjustments. Nevertheless, gastric cancer is still prevalent in parts of the world where fresh food storage and water quality are inadequate. Most cases of stomach cancer are found in underdeveloped nations; men are twice as likely to get it as women are, and black men are more likely to get it than white men. Higher socioeconomic status white Western society has the lowest occurrence.

Because second and third generation Americans had lower incidence of stomach cancer than other generations, migration studies have provided evidence that lifestyle modifications have an impact on the development of stomach cancer. Previous theories of stomach cancer provide compelling evidence that medical, dietary, and social factors-rather than hereditary predisposition—have been linked to the disease in Japanese migrants. The histological patterns of gastric cancer have also changed epidemiologically; in contrast, the intestinal gastric type of the disease is gradually declining but is still more common (70%) than other types. It is typically observed in men with associated environmental variables who are older than fifty. On the other hand, the diffuse or infiltrative kind is less common (30%), but it also has a worse prognosis and is detected in both sexes at a younger age. The rising incidence of distal

esophageal carcinoma in the US is accompanied by a significant structural shift from distal to proximal stomach cancer. In Western countries, the most common sites are the proximal lesser curvature, heart, and esophagogastric junction (EGJ), but non-proximal still predominates in Japan. Compared to the United States, Japan has a much better prognosis for gastric cancer, mostly because of endoscopic screening programs that help identify lesions at an early and potentially treatable stage. [32-34]

Pathophysiology:

According to Lauren's histopathologic categorization, gastric adenocarcinoma has two primary histologic variations. The most common kind is known as the "intestinal type," so named due to its morphologic resemblance to intestinal tract adenocarcinomas. The diffuse-type gastric cancer is less prevalent and is distinguished by the absence of intercellular adhesions, which interfere with the development of glandular structures.

History and Physical Examination:

When they first show, most patients exhibit symptoms that indicate an advanced stage. Non-specific weight loss, chronic abdominal pain, dysphagia, hematemesis, anorexia, nausea, early satiety, and dyspepsia are some of the symptoms that present as gastric malignancies. Patients who arrive with a locally advanced or metastatic disease typically have severe abdominal discomfort, maybe ascites, weight loss, exhaustion, and visceral metastases on scans. They may also have an obstruction of the gastric outlet.

The most frequent physical examination finding that indicates advanced disease is a palpable abdominal mass. Additionally, the patient may exhibit Virchow's node (left supraclavicular adenopathy), Sister Mary Joseph's node (peri-umbilical nodule), and Irish node (left axillary node) as indicators of metastatic lymphatic dissemination distribution. Ascites

(peritoneal carcinomatosis), hepatomegaly (frequently diffuse disease load), Blumer's shelf (cul-de-sac mass), and Krukenberg's tumor (ovary mass) are some of the symptoms of direct metastasis to the peritoneum.

Skin conditions such as diffuse seborrheic keratosis or acanthosis nigricans, haematological conditions such as microangiopathic haemolytic anaemia and hypercoagulable state [Trousseau's syndrome], renal conditions such as membrane nephropathy, and autoimmune conditions such as polyarteritis nodosa are examples of paraneoplastic manifestations. None of these conditions is unique to stomach cancer.[35]

Evaluation:

A barium study should be performed during an upper endoscopy on patients who exhibit any symptoms suggestive of stomach cancer, except for restricted plastic that manifests as a leather-flask look. Despite being more expensive and invasive, upper endoscopy provides tissue diagnosis through direct biopsy of lesions in the duodenum, stomach, or esophagus. For increased diagnosis accuracy, each worrisome stomach ulcer should be biopsied more than once (one biopsy versus seven versus 98%) in terms of sensitivity. Only in regions with high cancer prevalence (Japan) has upper endoscopy screening for stomach cancer been able to successfully identify early stages with greater cure rates following resection.

A new staging scheme based on tumor, node, and metastasis (TNM) with 5-year overall survival (5-y OS) according to pathological stage and intervention (surgery only IA-93. 6%, IIA-81. 8%, and IIIA-54. 2% or with neoadjuvant I-76. 5%, II-46. 3%, III-18. 3%, and IV-5. 7%) has been outlined in the Eight Edition 2017 of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC).

Chest and abdominal imaging are part of the staging pre-preoperative examinations, which are used to rule out metastases and assess surgical resectability. With an overall accuracy

of 42% to 82%, abdominal-pelvic computed tomography is used early to rule out gross metastatic illness, although it is inaccurate in assessing T, N, and tiny peritoneal metastases. Although it depends on the operator, endoscopic ultrasonography aids in precise staging because of its superior diagnostic accuracy for tumor depth (57% to 88%) and lymph node status (30% to 90%). Biopsies ought to validate dubious single or oligometastatic locations; conversely, paracentesis ought to be executed in case malignant ascites is presumed. A simple radiograph is not favoured over a chest computed tomography (CT). In certain instances, positron emission tomography in conjunction with computed tomography imaging can assist in determining the resectability of stomach tumors (T2N0) if the previous staging examination is negative for the metastatic illness. The glycoprotein CA 125 antigen, carbohydrate antigen 19-9, cancer antigen 72-4, and carcinoembryonic antigen are serum indicators of limited value that can have increased levels from other sources. Before surgery, staging laparoscopy with peritoneal cytology examination is advised in the absence of apparent spread, especially for clinical stages greater than T1b. Patients undergoing preoperative therapy are also advised to undergo this procedure. Surgery is not advised if there is a positive peritoneal cytology and no discernible peritoneal spread, as this is an independent predictor of a high rate of recurrence following curative resection.

Human epidermal growth factor receptor 2 (HER2) gene amplification has been observed in 12% to 27% of cases of gastric cancer, whereas protein overexpression has been reported in 9% to 23% of cases. Although the exact effects of HER2 positive are yet unknown, it has been linked to decreased survival and tumor invasion as well as lymph node metastases. For all metastatic gastric cancers, HER2 testing is advised. The initial step in this process is immunohistochemical scoring, which is negative for 0 or 1+ and positive for 3+. Reflex, fluorescence, and in situ hybridization are then used to validate an equivocal 2+ score. Patients with solid tumors, such as stomach cancer, who exhibit microsatellite instability may benefit

from immunotherapy if their disease has spread and they have not responded well to conventional treatment. Epstein-Barr virus (EBV)-positive stomach cancers have a better prognosis; nonetheless, conventional clinical care does not yet suggest EBV staining. [36-41]

Figure 3: Stomach Taken for Bailey

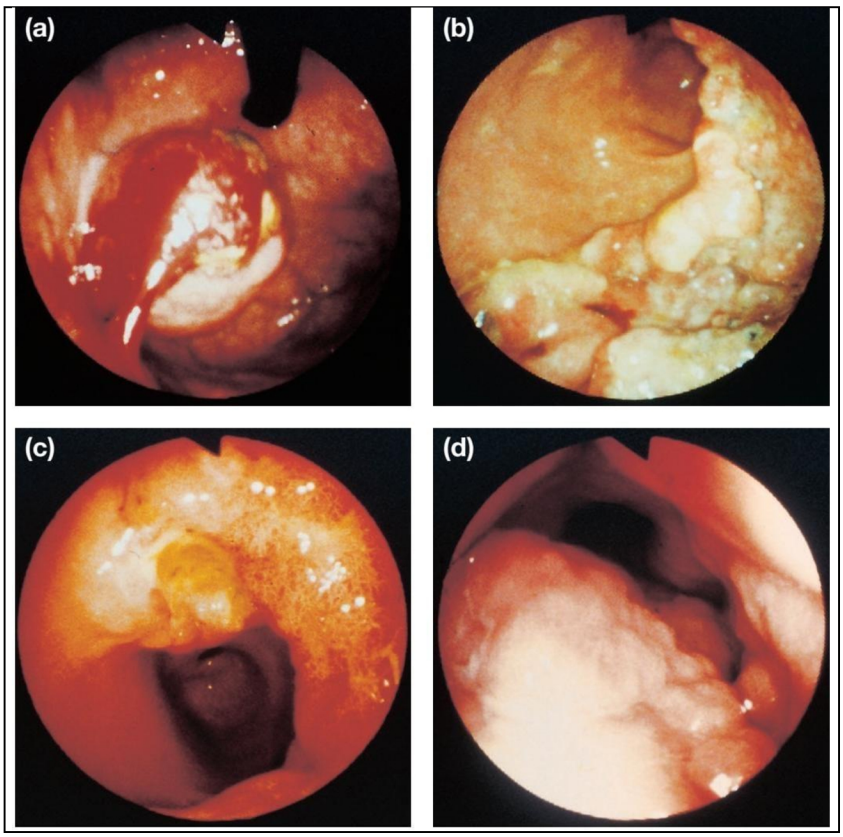


Figure 4: Advanced gastric cancer Bailey and love 28th edition, part 11 Chapter 66

Treatment / Management:

Treatment modality for gastric cancer depends on accurate preoperative staging. Therapeutic approach can be endoscopic resection for superficial, limited mucosa disease (< T1b, N0), upfront surgical resection with lymphadenectomy (< T3, any N), neoadjuvant (> T2) / adjuvant (> T1N1 or > T3N0) chemotherapy, radiation therapy, or combined with resectable lesions or palliative systemic therapy for those with locally advanced unresectable or metastatic disease (T4, any N, or M1).

Endoscopic Resection for Early Local Disease

Endoscopic resection either by endoscopic mucosal resection or endoscopic submucosal resection is offered to select patients with early gastric cancer with negative lymph nodes who meet selection criteria at centres of expertise. Standard selection criteria have a high-probability of en bloc resection, intestinal-type adenocarcinoma confined to the mucosa/submucosal, and absent venous or lymphatic invasion and tumors with diameters less than 20 mm without ulceration or 10 mm nonpolypoid flat or depressed lesions. Expanded criteria are under active investigation. Ten percent of mucosal and 20% of submucosal lesions will have lymph node metastasis and should be investigated carefully. If prior criteria are not met or an incomplete resection is performed, patients are referred for gastrectomy with regional lymph node resection. Successful endoscopic resection may offer a 5-year overall survival of 84% to 96% depending on the tumor's depth compared to gastrectomy survival rates up to 98%, but no randomized trials have compared both. Synchronous or metachronous gastric cancers can be found within 5 years in up to 9.2% of patients. *H. pylori* have been associated with metachronous gastric lesions, and eradication is recommended. Surveillance after endoscopic resection is the same strategy as for advanced cancer (detailed below). [43,44]

Surgical Resection for Resectable Disease

Patients with localized, resectable gastric cancer have the best chance of long-term survival with surgery alone. The main goal of surgery is complete resection with adequate margins (more than 4 cm), and only 50% of patients will obtain R0. Unresectability criteria are an invasion of major vasculature structure (aorta, hepatic artery, celiac axis, or proximal splenic artery), bulky adenopathy outside the surgical field, and the presence of linitis plastica; although, the latter is debatable. Most surgeons prefer total gastrectomy, but the technique depends on location, with proximal lesions requiring total resection and some distal lesions partial resection. Large mid-gastric lesions or diffuse disease should be offered a total gastrectomy. Routine or prophylactic splenectomy should be avoided. Standard surgical techniques in Japan, characterized by a better cancer survival, includes D2 resection (meticulous resection of all regional lymph nodes), which differs from the conservative type of lymphadenectomy performed in the United States, which carries less operative morbidity and mortality (standard D1 resection, removal of only peri-gastric lymph nodes). Two large trials by the Dutch Cancer Group and the Medical Research Council, comparing D1 with D2 lymphadenectomy, were flawed and underpowered to show D2 benefit. However, after a median 15-year follow-up of a 1078-patients in the randomized Dutch trial, D2 lymphadenectomy was associated with lower locoregional recurrence (12% versus 22%), regional recurrence (13% versus 19%), and gastric cancer–related death rates (37% versus 48%) than D1 surgery. Although D2 dissection was associated with significantly higher operative morbidity (10% versus 4%), complication rate (43% versus 25%), and higher reoperation rate (18% versus 8%) than D1 surgery. Considering a safer spleen-preserving D2 resection technique is currently available in high-volume centres, D2 lymphadenectomy is the recommended surgical approach for patients with resectable (curable) gastric cancer. D3 super-extended lymphadenectomy, including periaortic dissection, showed no added survival benefit

with significantly worse perioperative complication rate in the multi-centre Japan Clinical Oncology Group (JCOG) study 9501. While the optimal extent of lymphadenectomy is debated, current guidelines recommend 15 lymph nodes or more sampling, which showed a survival benefit. A high-volume centre of excellence may offer laparoscopic resection instead of open gastrectomy, with a 5-year overall survival (OS) of 58.9% and 55.7%, respectively. Palliative resection, even with positive margins, is acceptable for symptomatic disease (obstruction or uncontrolled bleeding). [45,46]

Neoadjuvant and Adjuvant Therapy for Locally Advanced Resectable Disease

Surgical resection alone is potentially curative but only in early gastric cancer stages as seen in long-term survival rates on reported 5-year overall survival. It significantly declines from 75% for stage I to 35% for stage II and 25% or less for stage III, pushing research efforts to improve results using neoadjuvant (preoperative) or adjuvant (postoperative) therapies. Neoadjuvant chemotherapy has been shown to downstage primary tumors and regional lymph nodes to attempt higher long-term curative resections.

Palliative Therapy for Locally Advanced Unresectable and Advanced Metastatic Disease

Unresectable locally advanced gastric cancer is often treated with advanced metastatic disease therapy regimens. The goals of medical treatment of advanced gastric cancer are primarily palliative symptoms, improve quality of life, and modest life-prolonging effect of weeks to months. Multiple agents are active in gastric cancer, including fluoropyrimidines (fluorouracil, capecitabine, and S1), anthracyclines (epirubicin), platinum agents (cisplatin and oxaliplatin), taxanes (paclitaxel and docetaxel), irinotecan, and other targeted therapies, including trastuzumab for *HER2*-overexpressing gastric cancers and ramucirumab, a VEGFR2 antibody. Combination regimens are associated with an increased response rate of up to 65% compared with single-agent therapies up to 40%.

Recent advances in treatment of Gastric Carcinoma:

1. **Targeted Therapies**:

- HER2 Targeting: Trastuzumab, a monoclonal antibody targeting HER2, has significantly improved outcomes in HER2-positive gastric cancers when combined with chemotherapy.
- EGFR Inhibitors: Drugs like cetuximab and panitumumab are being studied for their potential in treating gastric cancer, particularly in EGFR-overexpressing tumors.

2. **Immunotherapy**:

- PD-1/PD-L1 Inhibitors: Drugs such as pembrolizumab, nivolumab, and atezolizumab have shown promise in treating advanced gastric cancers, particularly in patients with PD-L1-positive tumors or MSI-high status.
- Checkpoint Inhibitors: These therapies aim to enhance the immune system's ability to recognize and attack cancer cells.

3. **Radiation Therapy Advances**:

Intensity-Modulated Radiation Therapy (IMRT) and Proton Therapy: These techniques offer more precise targeting of tumors while minimizing damage to surrounding healthy tissue, reducing treatment-related toxicity.

HUMAN PAPILLOMA VIRUS (HPV)

With over 150 genotypes, HPV is a non-enveloped DNA virus that is a member of the papillomaviridae family. Low copy levels of HPV DNA have been found to be integrated in the glandular epithelium of cervical adenocarcinoma, OAC, and its precursor lesion, Barrett's

dysplasia (BD), despite the fact that it exhibits tropism for squamous epithelium.[42–44] They are divided into low-risk (HPV-6 and 11) and high-risk (HPV-16 and 18) groups according to their potential to alter host cells and accelerate the development of cancer.[45–46] Cervical squamous carcinoma is the finest example of HPV carcinogenesis, as micro-abrasions inflict an infection on the basal cell layer, which can lead to either a benign or malignant lesion, or a sub-clinical infection. One important stage in the origin of cancer is assumed to be the integration of HPV DNA into the host genome.[47] Integration may promote oncogenesis by upregulating the production of cellular oncogenes, primarily E6 and E7.[48] The integration of the viral genome causes the repressive E2 gene to be expressed erratically, which in turn promotes the aberrant and continuous production of E6 and E7 oncoproteins.[49] E7 triggers the proteosome-dependent degradation of the retinoblastoma tumor suppressor protein (pRb) and inhibits it. E6 causes the p53 to be degraded and increases the expression of telomerase, which gives altered cells an endless lifespan.[50] It is now widely acknowledged that HPV is the cause of anal neoplasia, oropharyngeal cancer, and cervical cancer.

Combination regimens are associated with an increased response rate of up to 65% compared with single-agent therapies up to 40%.

Tumour virology was born with the discovery by Peyton Rous in 1911 of a filterable agent in chicken cellular extracts that caused neoplasia in healthy chickens. Universally, 20% of all human cancers have a viral aetiology. Viruses are involved at various stages of the carcinogenesis pathway, depending on the viral pathogen, and likely require co-factors. Multiple risk factors have been associated with esophageal and gastric malignancy, including carcinogenic pathogens. These viruses and bacteria include human papillomavirus (HPV) [esophageal cancer], Epstein–Barr virus (EBV) [proximal stomach cancer], and Helicobacter pylori (HP) [non-cardia stomach cancer]. Viruses such as EBV have been firmly established as causal for up to 10% of gastric cancers. HPV is associated with 13 to 35% of esophageal

adenocarcinoma but its role is unclear in esophageal squamous cell carcinomas. The causal relationship between hepatitis B (HBV), cytomegalovirus (CMV), HPV, and John Cunningham (JCV) and gastric neoplasia remains indeterminate and warrants further study. The expression of viral antigens by human tumors offers preventive and therapeutic potential (including vaccination) and has already been harnessed with vaccines for HPV and HBV. Future goals include viral protein-based immunotherapy and monoclonal antibodies for the treatment of some of the subset of EBV and HPV-induced gastro-esophageal cancers.

EPSTEIN BARR VIRUS (EBV)

The first human tumor virus discovered in Burkitt's lymphoma cell cultures was EBV.[51] More than 90% of people worldwide are infected with HHV-4, a DNA herpesvirus that primarily causes asymptomatic infections.[52–53] EBV-1 and EBV-2 are the two subtypes of this lymphotropic and epitheliotropic virus, which are distinguished by changes in the sequence of the Epstein-Barr nuclear antigen.[54] Asia, Europe, and the Americas are home to the majority of type 1 infections, while Africa and New Guinea are primarily home to type 2 infections.[55] It is the cause of 1.5% of all cancers in humans worldwide, primarily lymphomas and nasopharyngeal cancers, but it also causes other malignancies that are not lymphoid, such as gastric cancer and leiomyosarcomas.[56] The International Agency for Research on Cancer has therefore designated EBV as a Class I carcinogen.[57]

EBV mostly affects the oropharyngeal epithelium, after which it multiplies and moves to B cells, creating a latent infection that oversees many cancers in humans. Three latency types (types I, II, and III) of the infection can be distinguished based on the pattern of viral gene expression; these kinds will be covered in more detail below under the subheading of EBV and stomach cancer. Important components of carcinogenesis include the viral genome's survival in malignant cells, the expression of certain latent genes, and co-factors including co-infections and comorbidities.

Pathophysiology of Esophageal carcinoma and EBV

Jenkins et al. presented the first report of EBV DNA identification in OSCC in 1996. They discovered that 1/16 of OSCC cell lines and 5/60 oesophageal tumor samples were positive using microdissected tumor samples. Mizobuchi et al. examined 12 cell lines of OSCC and 41 surgical tissues for the EBV EBNA-1 gene using PCR, but they detected none. In 36 surgically removed OSCC, Yanai et al.'s second Japanese study found no EBER (EBV encoded RNA) -1-positive cell using ISH. Similarly, an investigation conducted by ISH on 104 surgically removed OSCC in Thailand did not reveal any EBER-positive cancer cells. Wang et al. used ISH and PCR amplification for the EBV BamHI W fragment to analyze 51 paraffin-embedded OSCC samples (9 well differentiated, 31 moderately differentiated, and 11 poorly differentiated tumors) from a high-risk region in Northern China for EBER. The results were all negative. On the other hand, in a Taiwanese investigation, PCR revealed the presence of EBV DNA in 11/31 (35.5%) of OSCC patients. The EBER detection by ISH verified these findings. Awerkiew et al. examined the existence of EBER transcripts (ISH) and EBV DNA (PCR) in 72 OSCC, 40 OAC, and 43 OSCC from Russia. They discovered that while EBER transcripts were absent from tumor nuclei, EBV DNA was present in 34% of OSCC and 26% of OAC. However, out of the 24 cases with positive EBV DNA, 7 OSCC and 1 OAC had EBER transcripts found in the nuclei of lymphocytes infiltrating the tumor. As EBV did not persist in tumor cells, the authors correctly inferred a negative correlation. Another negative investigation, published by Hong et al., found no EBV DNA in 30 OSCC and 2 OAC cell lines. Wu et al.'s analysis of 164 esophageal cancers (151 OSCC and 13 undifferentiated tumors) for EBV produced the most convincing positive finding. Ten (6.1%) tumor specimens were shown to have both EBV EBER and LMP-1 proteins by both ISH and IHC. These proteins were only

found in undifferentiated carcinomas with significant lymphoid infiltration or poorly differentiated squamous cell carcinomas.

The inconsistent data (similar to that shown in OSCC and HPV) results from a mix of ethnic, regional, and detection method variations. It's also unclear if stringent precautions were made to avoid contamination. When using ISH, using outdated formalin-fixed tissue specimens can lead to RNA degradation and a higher false-negative result. However, it appears that a tiny percentage of OSCC are connected to EBV.

Pathophysiology Esophageal carcinoma and HPV

One type of cancer that typically affects men three to four times more frequently than women is esophageal cancer. Cancer can be classified into two main types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). While gender, cigarette smoking, gastroesophageal reflux illness (which can result in Barret's dysplasia, or BD), and obesity are the key risk factors for EAC, increasing age, male sex, cigarette smoking, and alcohol intake are the main risk factors for ESCC. Although numerous Chinese research have already revealed favourable links between those two factors, studies from Western countries typically report no apparent associations, raising doubts about the role of the human papillomavirus (HPV) in the start of ESCC. This could indicate that there is no way to rule out HPV DNA contamination as the reason for the high HPV prevalence in ESCC tissue. A robust correlation between high-risk HPV and both BD and EAC was demonstrated by Rajendra et al. 81 patients out of 261 were positive for HPV DNA. In both the BE and the controls, HPV was primarily found at the transition zone. In BD (68. 6%, incidence rate ratio (IRR) 2. 94, 95% confidence interval (CI) 1. 78–4. 85, $p < 0.001$) and EAC (66. 7%, IRR 2. 87, 95% CI 1. 69–4. 86, $p < 0.001$), HPV positive was substantially more prevalent than in controls (18. 0%). They looked into whether there was a noticeable genetic difference between HPV-positive and HPV-negative EAC based

on the study's findings. In comparison to the patients with esophageal cancer who were virus-negative, the HPV-positive cohort had almost 50% fewer non-silent somatic mutations (1. 31 mutations/Mb vs. 2. 56 mutations/Mb, p = 0. 048). There has been a meta-analysis looking at the connection between HPV infection and overall survival from esophageal cancer. It suggested that when assessing the risk factors for esophageal cancer, HPV infection could not be a useful prognostic indicator. The two primary components of treatment for esophageal cancer are surgery and neoadjuvant concurrent chemoradiotherapy (CCRT). For patients with locally advanced esophageal cancer, randomized trials have shown a strong boost in survival rate when neoadjuvant chemotherapy and radiotherapy are used in conjunction with surgery. According to Bognar et al., HPV infection is a poor prognostic factor for patients with ESCC because it has been linked to both a poor response to oncological treatment and a lower overall survival. Thus, it is now unable to definitively establish a link between HPV infection and esophageal cancer. The before mentioned research's findings suggest that there may be a link between the prevalence of HPV and the incidence of EAs, however trustworthy information regarding HPV's effect on ESCC appears to be lacking. More research must be done on this matter.

Pathophysiology of gastric carcinoma and EBV

Since its initial isolation from Burkitt's lymphoma biopsies, the Epstein-Barr virus (EBV) has been connected to several epithelioid disorders. EBV replication can result in lesions like hairy leukoplakia. It is already well known that EBV and nasopharyngeal carcinoma are strongly associated (see G. Niedobitek, this issue). Additionally, the development of in situ hybridization (ISH) and polymerase chain reaction (PCR) techniques demonstrated the connection between EBV and numerous additional cancers, such as gastric adenocarcinoma.

Worldwide, monoclonal proliferations of EBV-infected gastric cancer cells account for about 10% of gastric carcinoma cases.

In vitro, epithelial cells have demonstrated an impressive resistance to EBV infection, in contrast to B cells. This has made it more difficult to research how EBV contributes to the growth of epithelial cancers. When combined with the observation that all carcinoma cells in gastric carcinomas that test positive for EBV are also positive for EBV, these data imply a significant role for EBV in the formation of cancer.

When using EBER ISH to examine the dysplastic mucosa around tumors in non-neoplastic gastric mucosa, scattered EBV positive cells are seen. However, these cells are not present in the normal gastric mucosa, intestinal metaplasia, adjacent lymphocytes, or other normal stromal cells. These findings imply that EBV infection happens throughout the dysplastic period and that the virus appears to confer a growth benefit. Additionally, although EBER expression was not observed, a sensitive DNA ISH technique demonstrated that non-neoplastic gastric epithelium, including intestinal metaplasia, is commonly infected with EBV. Recently, the tissue of hepatocellular cancer was reported to exhibit a comparable EBER negative EBV latency. These findings imply that gastric epithelium may serve as an EBV reservoir and emphasize the risk of using EBER detection as the only indicator of latent EBV infection.

EBV-specific immunity in cancer patients High IgG antibody titres against EBV capsid antigens (VCAs) and early antigens (EAs) are present in patients with gastric cancer that is EBV positive. About 60% of patients have IgA antibodies against VCAs, yet their diagnostic utility is restricted because their titres are significantly lower than those of nasopharyngeal cancer. Prior to the diagnosis of EBV-positive gastric cancer, there is proof of elevated antiviral titres.[24] Although EBV specific cellular immunity is not significantly decreased, these results

are comparable to other EBV linked malignancies and indicate that active EBV infection exists prior to the formation of EBV positive gastric cancer.

Gastric adenocarcinomas linked to EBV frequently have a comparatively robust lymphocyte infiltrate. Mostly confined by the human leucocyte antigen (HLA) class I, these tumour infiltrating lymphocytes (TILs) are CD8 positive cytotoxic T lymphocytes (CTLs) that destroy autologous EBV immortalized cells (but not phytohemagglutinin blast cells). These findings indicate that the strong T cell response may be influenced by certain EBV-induced proteins, but that the reaction itself is a factor in the development of vesicular cancer. In gastric carcinoma, p53 overexpression and mutation are frequently found in precancerous dysplasia and metaplasia areas in addition to cancerous regions. This implies that the p53 mutation may be a precursor to stomach cancer. When compared to EBV negative cases, gastric carcinomas that are EBV positive typically express significantly more p53. According to Leung et al., almost all gastric carcinomas that are positive for EBV display weak to moderate levels of p53 in a varied percentage of carcinoma cells. This suggests that EBV may have a role in p53 overexpression through a non-mutational process. A similar theory has also been put out for nasopharyngeal carcinoma, where sequencing analysis has not been able to identify p53 mutation despite most patients showing p53 overexpression.

Compared to EBV negative cases, there are less apoptotic tumor cells in gastric carcinomas that are EBV positive. In gastric cancer with EBV positivity, high bcl-2 expression may shield tumor cells from dying. An infection with Helicobacter pylori causes intestinal metaplasia after persistent atrophic gastritis, and it is epidemiologically associated with gastric cancer. 34 In both EBV positive and EBV negative instances, intestinal metaplasia and atrophic mucosa encircle the gastric cancer tissues. It is possible that EBV infection develops in atrophic epithelial cells and causes the development of cancer. The frequency of H pylori infection does not significantly differ between gastric carcinomas that are EBV positive and negative.

Carcinomas are common in the residual stomach following a partial gastrectomy for benign conditions. 36 This is known as stump cancer or gastric residual cancer. The longer the postoperative recovery period, the higher the cancer risk. The high danger has been explained in several ways. Mucosal cell growth is stimulated by prolonged exposure to pancreatic secretions and alkaline bile reflux. Compared to non-remnant carcinomas, the prevalence of EBV involvement in remnant carcinomas is much higher (27%).

HPV and Gastric Cancer

Studies about the function of HPV in GC have shown conflicting results. Publications about associations, both positive and bad, abound. However, a recent meta-analysis of fourteen studies examining the prevalence of HPV in 1205 controls and 901 gastric cancer patients found that the former had a pooled prevalence rate of 23.6%. The risk of gastric cancer was significantly correlated with HPV infection (OR = 1. 53, 95% CI 1. 00–2. 33, p = 0. 002).[57]

The part viruses play in the development of cancer has long been a topic of intense discussion. It is insufficient to prove causation when viral DNA, RNA, or proteins are only detected. However, it is well recognized that viruses like EBV are the cause of up to 10% of stomach malignancies. Given the strength of positive association studies, the significance of HPV in a sizable percentage of OAC is becoming more well acknowledged, however it is more debatable for OSCC.[57]

CLINICAL STUDIES

Jafari-Sales et al. (2022) conducted a thorough investigation of the HPV and EBV prevalence in GC. It was assessed what the chances ratio was for EBV and HPV viruses in GC. Software known as SPSS (Version 20) was used to analyze the data. After the inclusion criteria were

obtained, sixty research including 14949 patients were included in the analysis. HPV and EBV virus prevalence in GC were 10. 58% and 8. 58%, on average, respectively. In Turkey and Iraq, the greatest HPV and EBV prevalences were 37. 74% and 44. 44%, respectively. Asia (17.54%) and Africa (19.02%) had the highest chances of HPV and EBV in GC, respectively. The results show that GC in the research locations has both HPV and EBV. Nevertheless, the current study's findings are insufficient to draw a more precise conclusion. Thus, more research is required to reach a conclusion in this area. [58–59]

Yahyaapour et al. (2018) investigated the presence of three oncogenic viruses in neoplastic and non-neoplastic esophageal lesions taken from Mazandaran, a high-risk region of Iran: the human papilloma virus (HPV), the Epstein-Barr virus (EBV), and the Merkel cell polyomavirus (MCPyV). A total of 168 esophageal specimens (68 without esophageal cancer and 100 with ESCC confirmed diagnosis) underwent Real Time PCR analysis for HPV, EBV, and MCPyV. According to the findings, HPV DNA was discovered in 28 of the 68 samples from the non-neoplastic group (41.2%) and 27 of the 100 neoplastic esophageal lesions (27.0%). Three of the 68 samples in the non-neoplastic group (4.4%) and 10 of the 100 neoplastic cases (10%) had esophageal specimens with EBV DNA found in them. MCPyV DNA was found in esophageal specimens from 24 of the 68 samples in the non-neoplastic group (35.3%) and 30 of the 100 neoplastic cases (30.0%). Between the groups with and without cancer, there was no statistically significant difference in HPV (p=0. 066), EBV (p=0. 143), or MCPyV (p=0. 471) DNA positive. This work disproves the theory that HPV, EBV, and MCPyV play a pathogenic role in the malignant transformation of the esophagus by demonstrating their detection in both neoplastic and non-neoplastic esophageal tissues.[60]

Sadeghi et al. (2024) used real-time PCR to assess the presence and viral load of HR-HPVs (HPV-16 and HPV-18) and EBV in 258 cervical samples, including both formalin-fixed paraffin-embedded (FFPE) and fresh cervical tissues. The study included Iranian women with

cervical intraepithelial neoplasia (CIN), squamous cell carcinoma (SCC), and a cervicitis control group. The results of the study showed a significant ($p<0.001$) relationship between greater HPV-16 positivity and co-infection with both HPV-16 and HPV-18 with the severity of the disease. It's interesting to note that compared to SCC/CIN groups, the control group had a greater frequency of EBV-positive patients ($p<0.001$). While HPV-18 revealed no significant difference ($P=0.058$), HPV-16 DNA load increased with disease severity ($P<0.01$). In comparison to the SCC/CIN groups, the control group's EBV DNA burden was greater ($P=0.033$). SCC, CIN II, and CIN III were all at higher risk with HPV-16, whereas CIN II and CIN III were more likely with HPV-18. Interestingly, EBV was linked to a decreased incidence of SCC and CIN groups. The authors came to the conclusion that there was no discernible variation in EBV co-infection with HPV-16/18, refuting the theory that EBV is a cofactor in CC. The control group's elevated EBV viral load, however, points to a possible "hit and run hypothesis" role in the development of CC. According to this theory, EBV might have a brief, early impact on the start of CC but then take a less active role in its continued development.[61]

In order to arrange the available data regarding the correlations between HPV infections and gastrointestinal malignancies, such as oropharyngeal, esophageal, gastric, colorectal, and anal cancers, Deniz et al. (2022) performed a review. This review, which took into account the majority of recent medical research, came to the conclusion that HPV infections may contribute to the oncogenesis of malignancies of the digestive system. It is possible that HPV is the cause of esophageal and oropharyngeal squamous cell malignancies. Nonetheless, there is less evidence linking HPV to colorectal and stomach cancers. Oropharyngeal and gastrointestinal cancers are typically multifactorial in nature, with HPV contributing to the formation of at least some of these tumors. Because of their high infection rate and risk for cancer, HPV infections present significant challenges.[62]

The study conducted by Milani et al. (2024) sought to examine the correlation between GIT and the following viruses: Epstein-Barr virus (EBV), Human Papillomavirus (HPV), John Cunningham Virus (JCV), and Cytomegalovirus (CMV). The study involved 81 patients with GIT cancers, such as stomach (n = 26), esophagus (n = 28), and colorectal (n = 27), and 81 subjects with gastrointestinal complaints who did not have GIT cancers. The research was carried out at two educational centers (the Shahem and Imam Reza hospitals) in Mashhad, Iran. Real-Time PCR was used to identify viral DNA. The findings showed that, in comparison to healthy control participants, patients with colorectal cancer (CRC) had considerably higher levels of JCV and HPV infections. In comparison to the control group, those with gastric cancer (GC) had far greater frequencies of HPV and EBV, and those with esophageal cancer (EC) had higher rates of JCV infection. When compared to the healthy patients, JCV infection dramatically raised the risks of CRC and EC incidence by 11. 8 and 10. 2 times, respectively. Furthermore, a 10.8- and a 6.7-fold increased risk of gastric cancer and colorectal cancer, respectively, was linked to HPV and EBV. The results of this study indicate that gastrointestinal malignancies may be associated with JCV, EBV, and HPV infections; gastrointestinal cancers did not exhibit any link with HSV or CMV.[63]

Jafari-Sales et al. (2023) collected 100 paraffin-embedded tissue samples from lab archives in East Azerbaijan province between April and October 2021. These samples included 50 samples of GC, 25 samples of benign gastric hyperplasia, and 25 samples of a control group. The study was a descriptive cross-sectional investigation to assess the presence of human papillomavirus (HPV) in GC by immunohistochemistry (IHC) and polymerase chain reaction (PCR) in hospitals in the province. The HPV virus was found using PCR and IHC. Data analysis was done using SPSS software version 22, the t-test, and Chi-Square statistical testing. Eight of the fifty cancer samples tested positive for HPV by PCR and IHC, according to the findings. The mean age of the HPV-positive samples was 62.87 ± 9.67. In comparison to

women, men had more HPV-positive samples than women (5 samples vs. 3 samples). Nevertheless, no viral genomes were found in the control or non-malignant samples. HPV infection and GC were significantly correlated (P=0. 03). The results of the study indicate that the development of GC in the hospitals in the province of East Azerbaijan is significantly influenced by the presence of HPV infection in GC. Additionally, because the results of IHC and PCR were identical, the results demonstrated that PCR and IHC are equally as sensitive and reliable in detecting HPV. For this reason, the IHC method can be used to find HPV oncoproteins instead of using the PCR method.[59]

To shed light on the correlation between EBV infection and gastric cancer, Tavakoli et al. (2020) conducted a meta-analytic evaluation of the prevalence of EBV in patients with gastric cancer. Using internet databases, a literature search for English-language articles was done electronically until July 1st, 2019. Using a random-effects model, the pooled EBV prevalence and 95% confidence intervals (CIs) were calculated. For case-control studies, the pooled odds ratio (OR) and its 95% confidence interval (CI) were calculated to ascertain the relationship between EBV and stomach cancer. To determine the pooled estimates of ORs, data from case-control studies using matched and non-match pairs designs were subjected to two distinct analyses. The combined prevalence of EBV in 20,361 individuals with gastric cancer was 8. 77% (95% CI: 7. 73–9. 92%; I2 = 83. 2%), according to the data. Twenty investigations, involving pairs of normal tissue next to the tumor and from 4116 individuals with stomach cancer, were conducted using matched pairs design. For studies using matched pairs design, the pooled ORs were 18. 56 (95% CI: 15. 68–21. 97; I2 = 55. 4%), whereas for studies using a non-matched pairs design, the pooled ORs were 3. 31 (95% CI: 0. 95–11. 54; I2 = 55. 0%). Male cases had a considerably larger proportion of EBV-associated gastric cancer (10. 83% vs. 5. 72%) than female cases did (P < 0.0001). Nevertheless, compared to males (14. 07; 95% CI: 10. 46–18. 93; I2 = 49. 0%), the pooled OR estimate for EBV-associated gastric cancer was

considerably higher in females (21. 47; 95% CI: 15. 55–29. 63; I2 = 0%) (P = 0. 06). EBV was more common in the body (11.68%) and cardia (12.47%) than in the antrum (6.29%) (P = 0.0002). The scientists concluded that an EBV infection increases the risk of stomach cancer by more than 18 times based on their findings. Men are less likely than women to acquire EBV-associated gastric cancer, even though male patients with the disease had a higher incidence of EBV than female patients. The results of the study demonstrated that utilizing normal tissues next to tumors as the control group yields more reliable and accurate conclusions on the connection between EBV infection and stomach cancer.[64]

The current investigation was carried out with the research premise that HPV and EBV are viral risk factors that can lead to gastric and esophageal cancer. Additionally, the null hypothesis asserts that there is no association between HPV and EBV and gastric and esophageal cancer.

MATERIALS & METHODS

MATERIALS AND METHODS

Source of Data

This is a prospective study conducted in R. L. Jalappa Hospital, Tamaka, Kolar, following approval from institutional ethical committee of R. L. Jalappa Hospital, Tamaka, Kolar, over a period of two year from Sep 2022 to Aug 2024. The study included positive patients of HPV and EBV in esophageal and gastric carcinoma presenting to the hospital, who fulfilled the inclusion criteria.

Methodology

Patients with early or advance carcinoma of esophagus and stomach who gave signed inform consent for participating the study in R. L. Jalappa Hospital, Tamaka, Kolar. The patients were explaining about the study objective, procedure and expected outcome in detail before the start of the study. Based on the following inclusion and exclusion criteria, the patients were included in the study -

Inclusion Criteria

1. All new and previously diagnosed cases of Esophageal carcinoma and Gastric carcinoma.
2. All patients who give consent for the above study

Exclusion Criteria

Sewart Class II carcinoma.

Sample Size

Sample size was calculated by using the proportion of EBV in subjects who had Gastric carcinoma was 4. 4% from the study by Vera genitsh et al. using the formula

Sample Size = $Z1\text{-}\alpha /2\ 2\ P\ (1\text{-}P)$

d^2

Where,

Z1-α /2 = is standard normal variate (at 5% type 1 error (P<0. 05) it is 1. 96 and at 1% type1 error (P<0. 01) it is 2. 58). As in majority of studies P values are considered significant below 0. 05 hence 1. 96 is used in formula.

P= Expected proportion in population based on previous studies or pilot studies

d= Absolute error or precision

P = 4. 4% or 0. 044

q = 95. 6% or 0. 956%

d = 7. 5% or 0. 075

Using the above values at 95% Confidence level a sample size of 29 patients were included in the study. With 10% nonresponse sample size of 29 + 2. 9 ≈ 32 minimum patients were included in the study.

Examination Protocol

All patients with carcinoma esophagus and stomach thorough history were taken and relevant investigations were done. Patients were planned for Upper GI endoscopy guided or surgery and Tissue Biopsy was taken from there. The tissue samples were given for histopathology where, tissue blocks were made and sent for evaluation of EBV & HPV. PCR test was run for both the viruses i. e. EBV & HPV.

Investigation carried for the patient was as follows: -

- Complete blood count (CBC)
- Renal function tests
- Liver function tests
- Serum electrolytes

- Chest radiograph / CT thorax
- CECT abdomen and pelvis
- Histopathological staging

Statistical Analysis

The SPSS software for Windows, version 17.0, was used to conduct the statistical analysis (SPSS, Chicago, Illinois). Categorical data were shown as absolute numbers and percentage, whereas continuous variables were shown as mean ± SD. Prior to statistical analysis, the normality of the data was examined.

The study encompassed both qualitative and quantitative variables. Quantitative variables were distinguished using measures of central tendency and dispersion, namely the Mean and Standard Deviation, whilst qualitative variables were reported numerically and as percentages. To assess the association between two qualitative variables, Chi-square and Fisher's exact tests were employed. Meanwhile, Independent t-tests were utilized to compare the means of two independent quantitative variables. Data analysis was conducted using SPSS version 20, with a confidence level set at 95%.

RESULTS

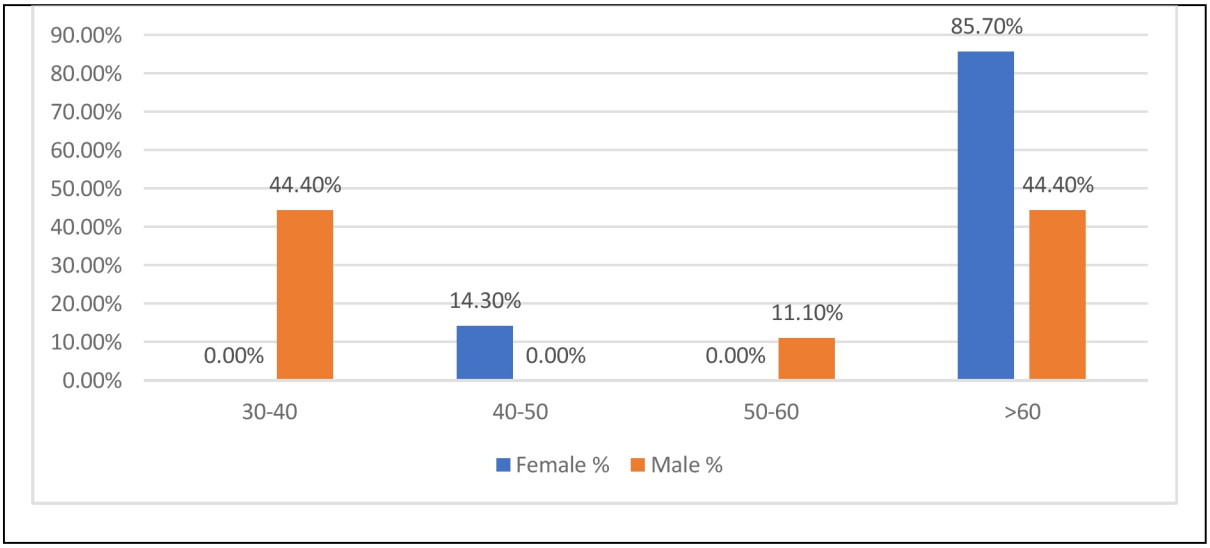
RESULTS

In the present study, there were a total of 32 cancer cases. Out of these, 16 (50%) were esophagus carcinoma and 16 (50%) were stomach carcinoma. Out of the total esophagus cases HPV positive was not observed in any case and HPV positive was found in 2(2. 5%) in gastric cases. EBV was positive in 5 (31. 2%) esophagus and 6 (37. 5%) gastric carcinoma cases.

Esophagus (n=16)

	Female		Male		Total
	N	%	N	%	
30-40	0	0. 0%	4	44. 4%	4
40-50	1	14. 3%	0	0. 0%	1
50-60	0	0. 0%	1	11. 1%	1
>60	6	85. 7%	4	44. 4%	10
	7	100. 0%	9	100. 0%	16

Table 1: Age and Gender wise Distribution



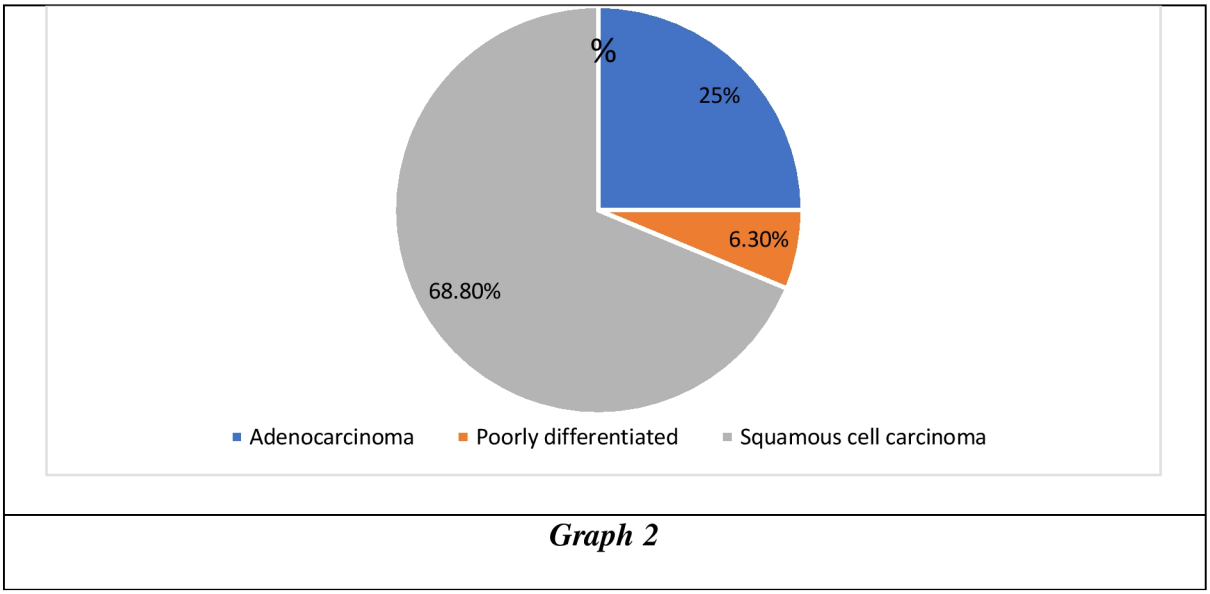
Graph 1

Table 1 presents the distribution of patients with exophages carcinoma by age and gender. Among the total 16 patients, males were more prevalent (56. 3%) compared to females (43. 8%). In the 30-40 age group, all 4 patients (44. 4%) were male. The 40-50 age group had only 1 patient, who was female (14. 3%). In the 50-60 age group, there was 1 male patient (11. 1%) and no females. In the >60 age group, females were predominant, with 6 patients (85. 7%), while males constituted 4 patients (44. 4%). This indicates a higher occurrence of exophages carcinoma in older females and younger males

Histopathology	**Frequency**	**Percent**
Adenocarcinoma	4	25. 0
Poorly differentiated	1	6. 3
Squamous cell carcinoma	11	68. 8
Total	16	100. 0

Table. 2 Details of Histopathology

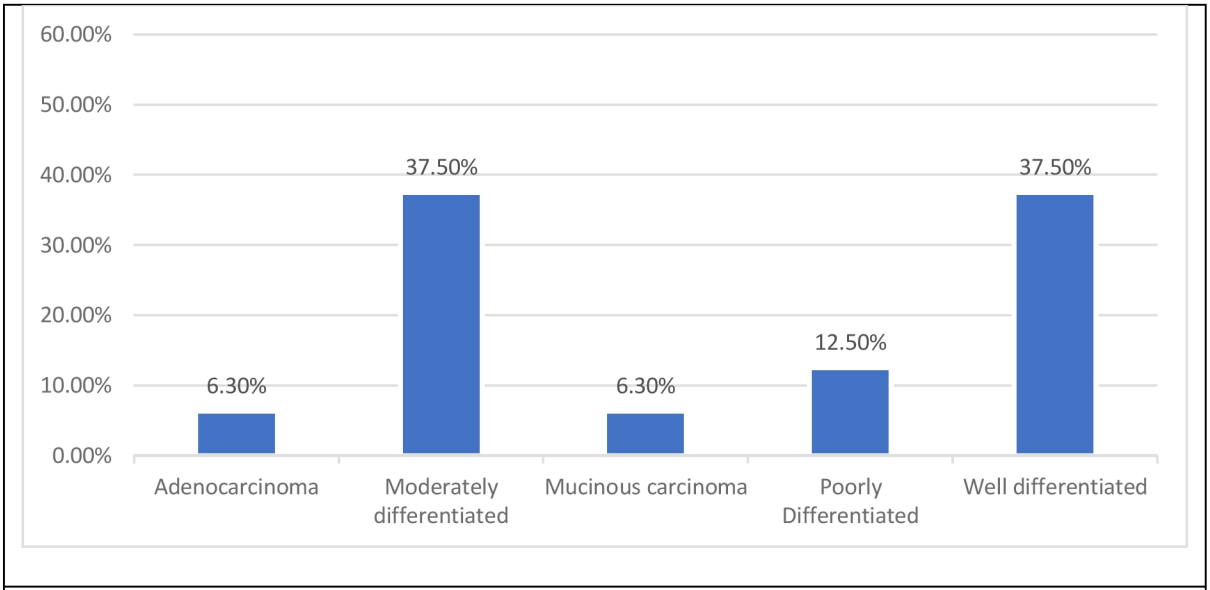
The histopathology data shows that among the 16 patients with exophages carcinoma, squamous cell carcinoma is the most common type (68. 8%), followed by adenocarcinoma (25. 0%), and poorly differentiated carcinoma (6. 3%). This indicates a predominance of squamous cell carcinoma in the patient population.



Graph 2

Differentiation	frequency	Percent
Adenocarcinoma	1	6. 3
Moderately differentiated	6	37. 5
Mucinous carcinoma	1	6. 3
Poorly Differentiated	2	12. 5
Well differentiated	6	37. 5
total	16	100. 0

Table 3: Details of Differentiation



Graph 3

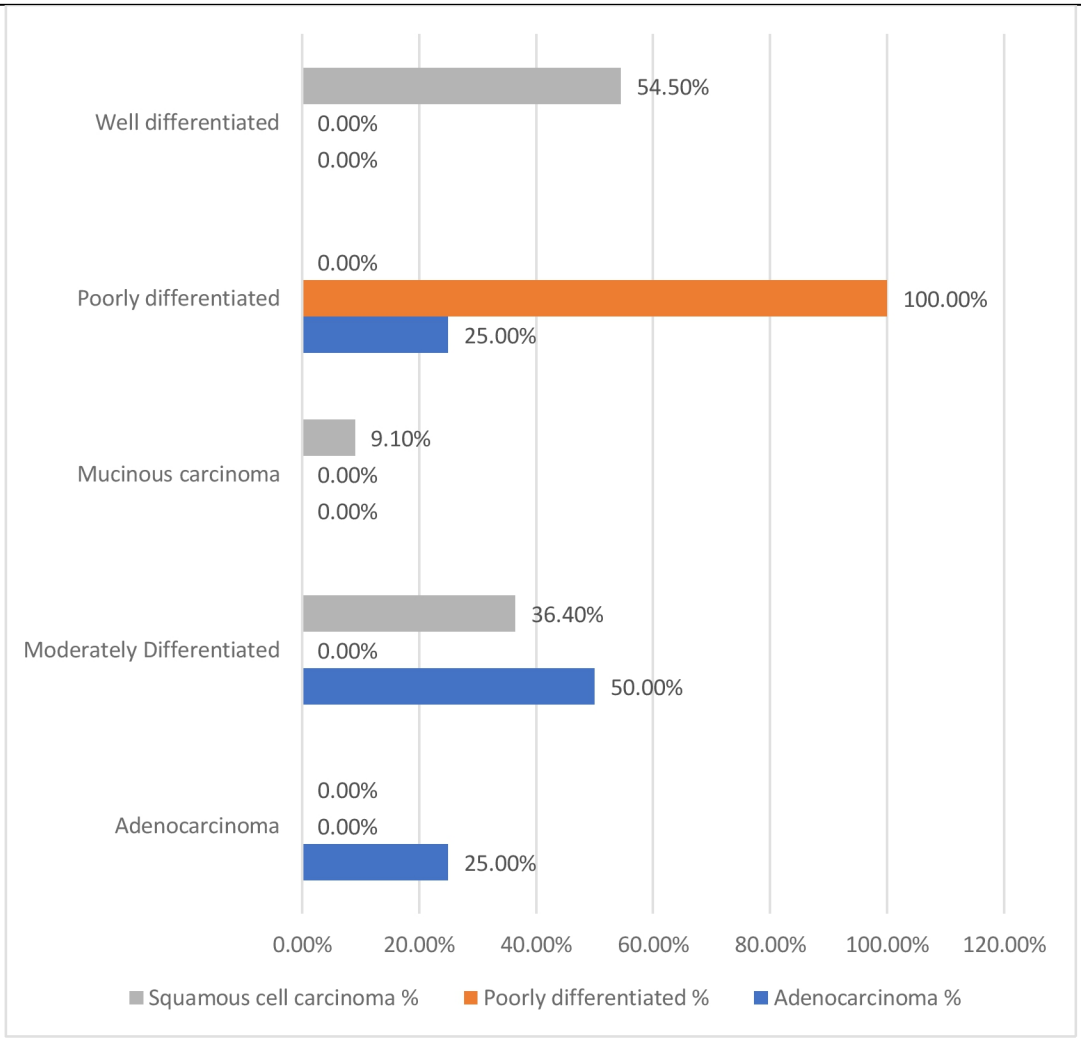
The data on differentiation among the 16 patients with exophages carcinoma shows that most cases are either moderately differentiated (37. 5%) or well differentiated (37. 5%). Poorly differentiated carcinomas account for 12. 5% of cases. Adenocarcinoma and mucinous carcinoma each represent 6. 3% of the total.

This distribution indicates that moderately and well-differentiated carcinomas are equally common among the patients, suggesting a relatively balanced differentiation profile. The lower frequencies of poorly differentiated and specific types like adenocarcinoma and mucinous carcinoma highlight their lesser prevalence in this patient group. Overall, the data points to a significant variation in the differentiation status of exophages carcinoma among the patients (for discussion)

Differentiation	Histopathology					
	Adenocarcinoma		Poorly differentiated		Squamous cell carcinoma	
	n	%	n	%	n	%
Adenocarcinoma	1	25. 0%	0	0. 0%	0	0. 0%
Moderately Differentiated	2	50. 0%	0	0. 0%	4	36. 4%
Mucinous carcinoma	0	0. 0%	0	0. 0%	1	9. 1%
Poorly differentiated	1	25. 0%	1	100. 0%	0	0. 0%
Well differentiated	0	0. 0%	0	0. 0%	6	54. 5%
total	4	100. 0%	1	100. 0%	11	100. 0%

Table 4: Details of association between Histopathology and differentiation

The data presents the distribution of histopathological types of exophages carcinoma according to their differentiation status. Among adenocarcinoma cases (n=4), 50. 0% are moderately differentiated, 25. 0% are poorly differentiated, and 25. 0% are well differentiated. For poorly differentiated carcinoma (n=1), it accounts for 100. 0% of the cases in its category. Squamous cell carcinoma (n=11) is predominantly well differentiated (54. 5%), followed by moderately differentiated (36. 4%), and mucinous carcinoma (9. 1%). No mucinous carcinoma or well-differentiated cases were observed in the adenocarcinoma group. This indicates that squamous cell carcinoma shows a higher prevalence of well-differentiated cases, whereas adenocarcinoma exhibits a broader range of differentiation.

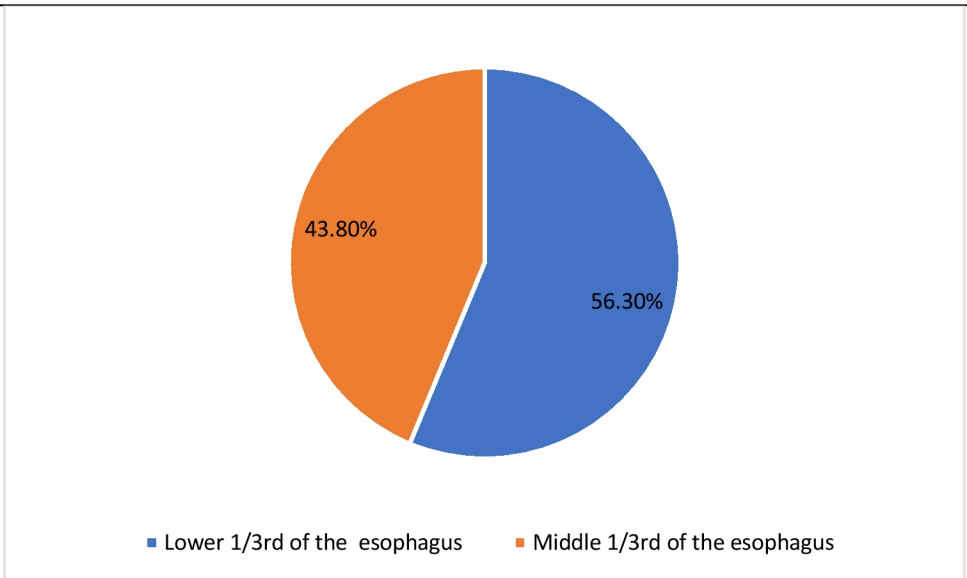


Graph 4

Area of Tumor	Frequency	Percent
Lower 1/3rd of the esophagus	9	56. 3
Middle 1/3rd of the esophagus	7	43. 8
Total	16	100. 0

Table 5: Frequency table of Area of tumor

The data on tumor location among 16 patients with exophages carcinoma reveals that 56. 3% of tumors are in the lower third of the esophagus, while 43. 8% are found in the middle third. This indicates a higher prevalence of tumors in the lower third of the esophagus.

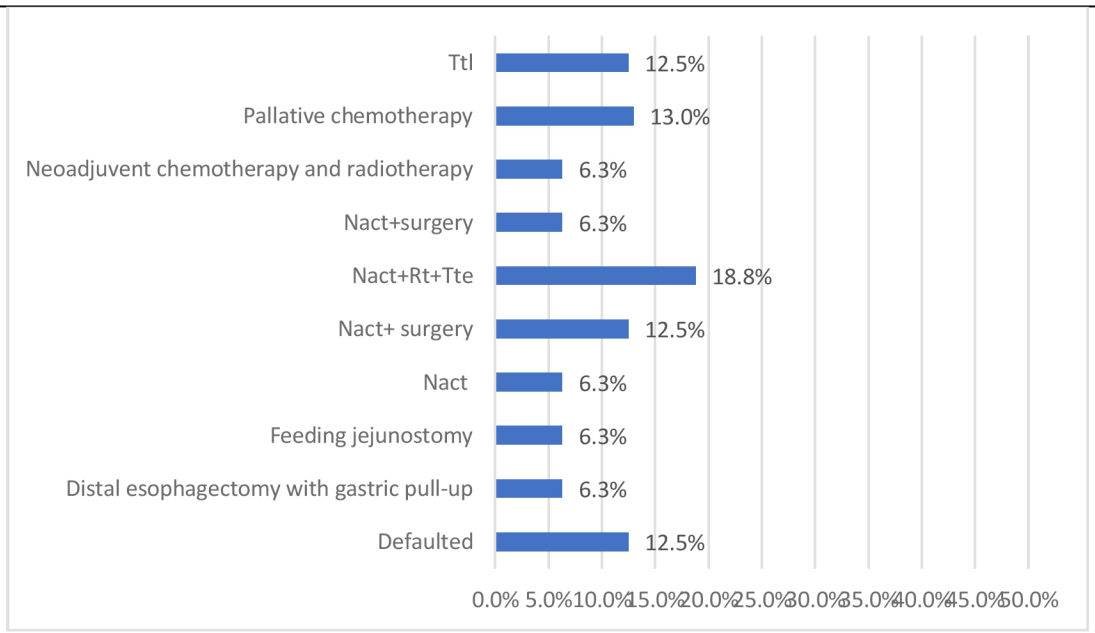


Graph 5

Mode of Treatment	Frequency	Percent
Defaulted	2	12. 5
Distal esophagectomy with gastric pull-up	1	6. 3
Feeding jejunostomy	1	6. 3
NACT	1	6. 3
NACT+ surgery	2	12. 5
TTE	3	18. 8
NACT + Surgery	1	6. 3
Neoadjuvant chemotherapy and radiotherapy	1	6. 3
Palliative chemotherapy	2	13. 0
TTE	2	12. 5
total	16	100. 0

Table 6: Mode Of Treatment in Esophageal Carcinoma

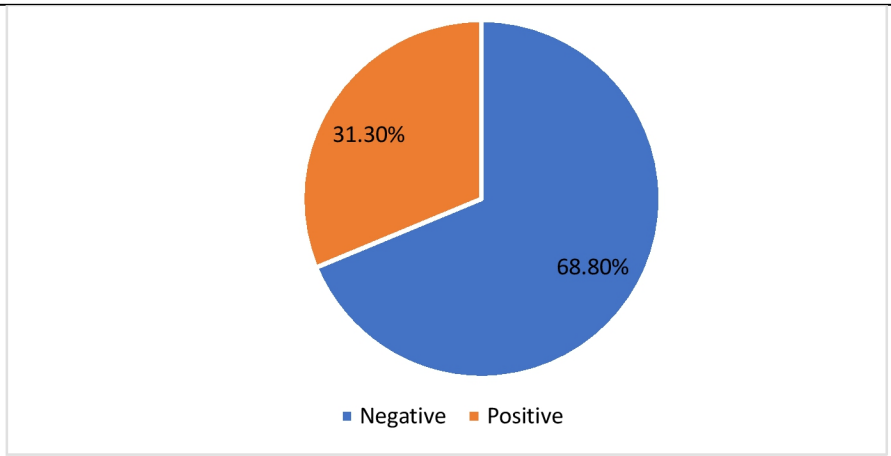
The treatment data for 16 patients with exophages carcinoma shows a variety of approaches. The most common treatment is NACT + RT + TTE (18. 8%), followed by defaulted treatment and NACT + surgery (both 12. 5%). Other treatments include distal esophagectomy, feeding jejunostomy, neoadjuvant therapies, and palliative chemotherapy,



Graph 6

EBV	Frequency	%
Negative	11	68. 8%
Positive	5	31. 3%
Total	16	100. 0

Table 7: EBV In Esophageal Carcinoma



Graph 7

		No. of Nodes Retrieved								Total
		3	**6**	**10**	**20**	**21**	**22**	**30**	**38**	
No of Nodes positive	1	0	0	1	0	0	0	0	0	1
	2	0	0	1	0	0	0	1	0	2
	3	1	0	0	0	0	0	0	0	1
	5	0	1	0	0	0	0	0	1	2
	6	0	0	0	0	1	0	0	0	1
	8	0	0	0	0	0	1	0	0	1
	10	0	0	0	0	0	1	0	0	1
	11	0	0	0	1	0	0	0	0	1
Total		1	1	2	1	1	2	1	1	10

Table 8: Association between No. of nodes retrieved and No. of nodes positive

Table presents data on the number of nodes retrieved and the number of positive nodes for each of those retrieved nodes across different scenarios.

- The first row indicates the number of nodes retrieved, ranging from 3 to 38.

- The subsequent rows represent the number of positive nodes found for each scenario of retrieved nodes.
- For instance, in the scenario where 3 nodes were retrieved, there was 1 positive node found.
- The last row provides the totals for each column.

Here is a summary of the data:

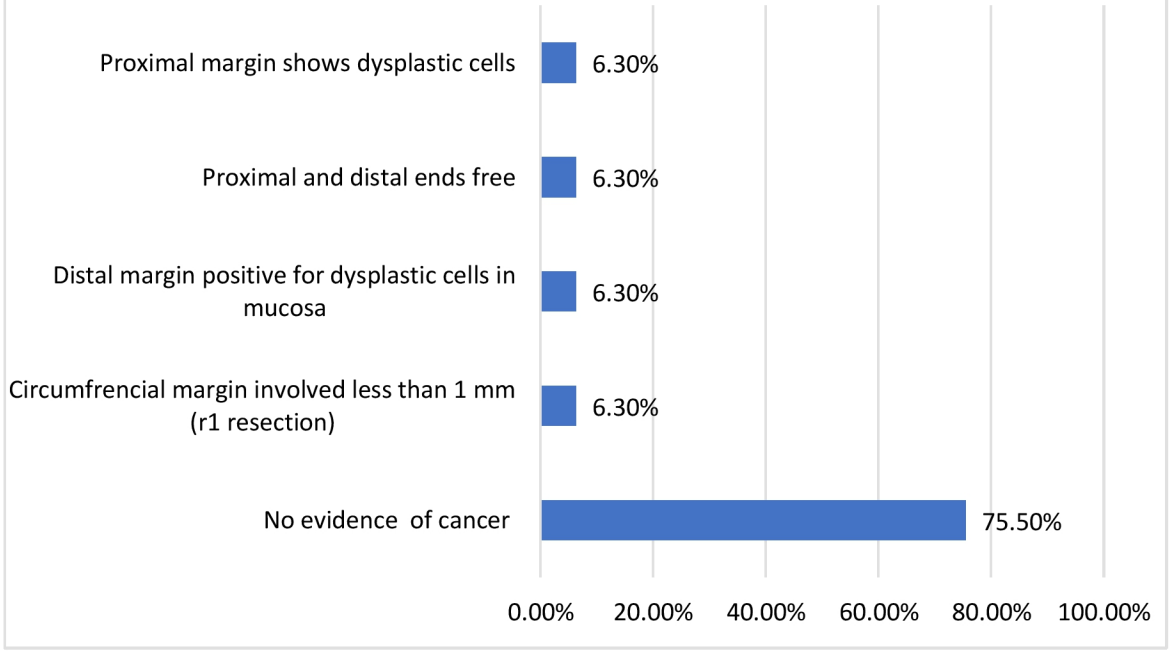
- For 3 nodes retrieved, 3 were positive.
- For 6 nodes retrieved, 5 were positive.
- For 10 nodes retrieved, 1& 2 were positive.
- For 20 nodes retrieved, 11 was positive.
- For 21 nodes retrieved, 6 was positive.
- For 22 nodes retrieved, 8 & 10 were positive.
- For 30 nodes retrieved, 2 was positive.
- For 38 nodes retrieved, 5 was positive.
- The total number of positive nodes found across all scenarios is 10.

Margins Positive	Frequency	Percent
No evidence of cancer	12	62. 5%
Circumferential margin involved less than 1 mm (r1 resection)	1	6. 3%
Distal margin positive for dysplastic cells in mucosa	1	6. 3%
Proximal and distal ends free	1	6. 3%
Proximal margin shows dysplastic cells	1	6. 3%

Table 9: Frequency table of Margine positive in the esophagus cases

The table 9 outlines margin statuses in a cancer assessment. The majority, 62. 5%, show

no cancer evidence. Other instances include marginal involvement, positive dysplastic cells, and negative margins, each comprising around 6. 3%. This breakdown indicates varying levels of involvement and highlights the importance of thorough examination for accurate diagnosis and treatment planning.



Graph 8

HPV	Frequency	Percent
NEGATIVE	16	100%

Table 10: HPV In Esophageal Carcinoma

This indicates that there were no positive cases of HPV detected in cases of esophagus.

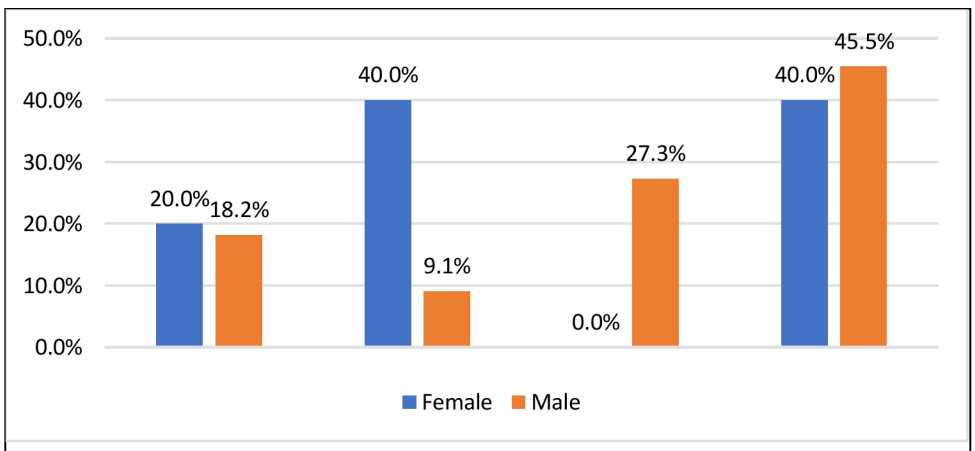
STOMACH

	Female		Male		Total
	N	%	N	%	
30-40	1	20. 0%	2	18. 2%	3
40-50	2	40. 0%	1	9. 1%	3
50-60	0	0. 0%	3	27. 3%	3
>60	2	40. 0%	5	45. 5%	7
	5	100. 0%	11	100. 0%	16

Table 11: Gender and age group wise distribution of cases

The table 11 presents demographic data categorized by age and gender. Each cell contains the count and percentage of individuals falling within specific age brackets. Notably, it reveals disparities in distribution between genders within certain age groups.

For instance, in the 30-40 age range, females constitute 20. 0% of the total, while males comprise 18. 2%. In the 40-50 bracket, females represent 40. 0% compared to males at 9. 1%. Conversely, in the >60 category, males make up 45. 5% of the total, surpassing females at 40. 0%.

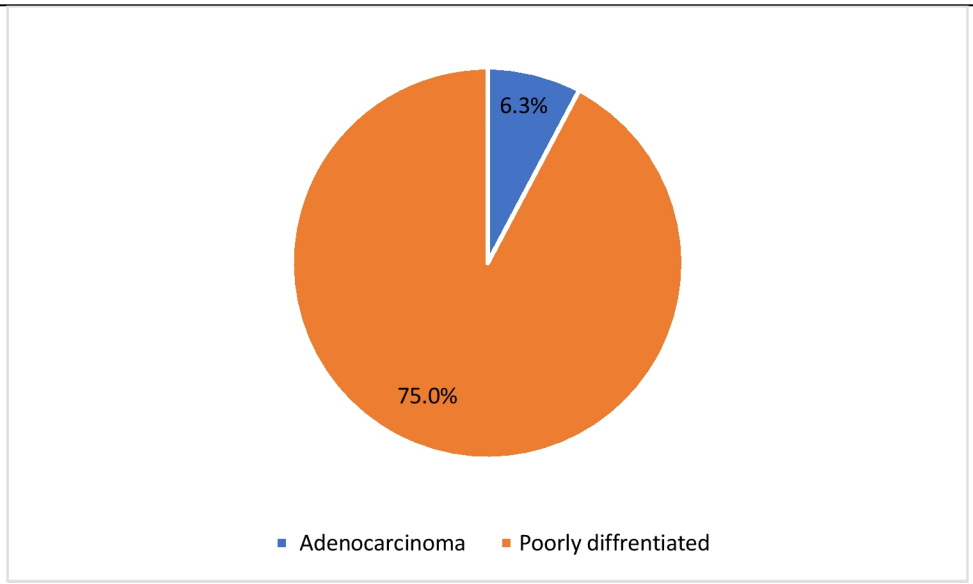


Graph 9

	Frequency	Percent
Adenocarcinoma	14	6. 3%
Poorly differentiated	2	75. 0%
Total	16	100. 0%

Table 12: *Details of Histopathology in Gastric Carcinoma*

Adenocarcinoma accounts for 14 cases, representing 6. 3% of the total, while poorly differentiated cases total 12, comprising 75. 0%. In sum, there are 16 cases, constituting 100. 0%. This breakdown highlights the prevalence of adenocarcinoma with a notable proportion showing poor differentiation.



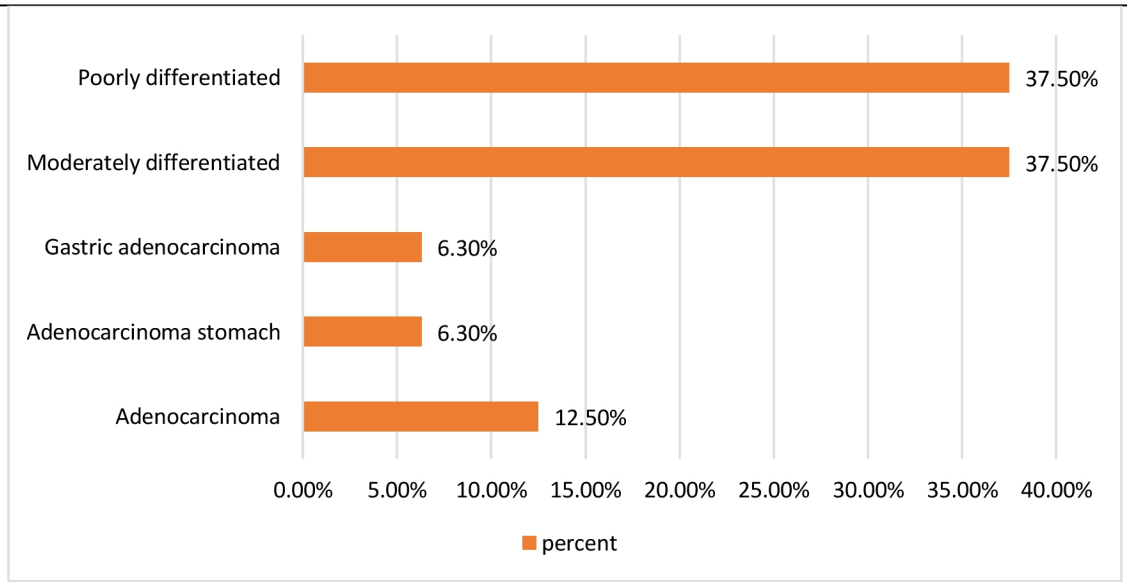
Graph 10

Differentiated	Frequency	Percent
Adenocarcinoma	2	12. 5%
Adenocarcinoma stomach	1	6. 3%

Gastric adenocarcinoma	1	6. 3%
Moderately differentiated	6	37. 5%
Poorly differentiated	6	37. 5%
total	16	100. 0%

Table 13: Frequency table of Differentiated in Stomach carcinoma

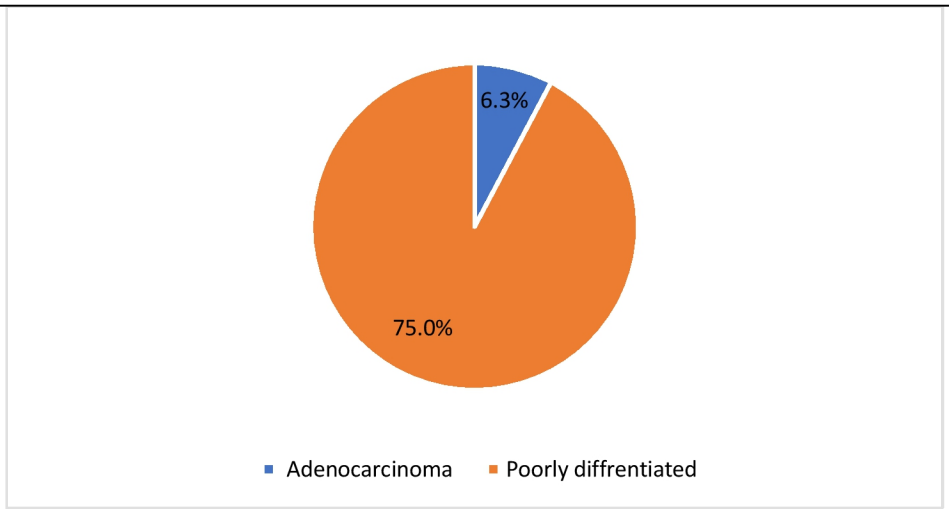
The table 13 presents the differentiation status of adenocarcinoma cases, detailing the frequency and percentage distribution within various subcategories. Notably, moderately, and poorly differentiated cases are equally prevalent, each comprising 37. 5% of the total cases, while adenocarcinoma with moderate differentiation represents the largest proportion. Adenocarcinoma, Adenocarcinoma stomach, and Gastric adenocarcinoma each contribute to smaller percentages, totaling 12. 5% collectively.



Graph 11

	Frequency	Percent
Adenocarcinoma	14	6. 3%
Poorly differentiated	2	75. 0%
Total	16	100. 0%

Table 14: Frequency table of Histopathology in stomach carcinoma



Graph 12

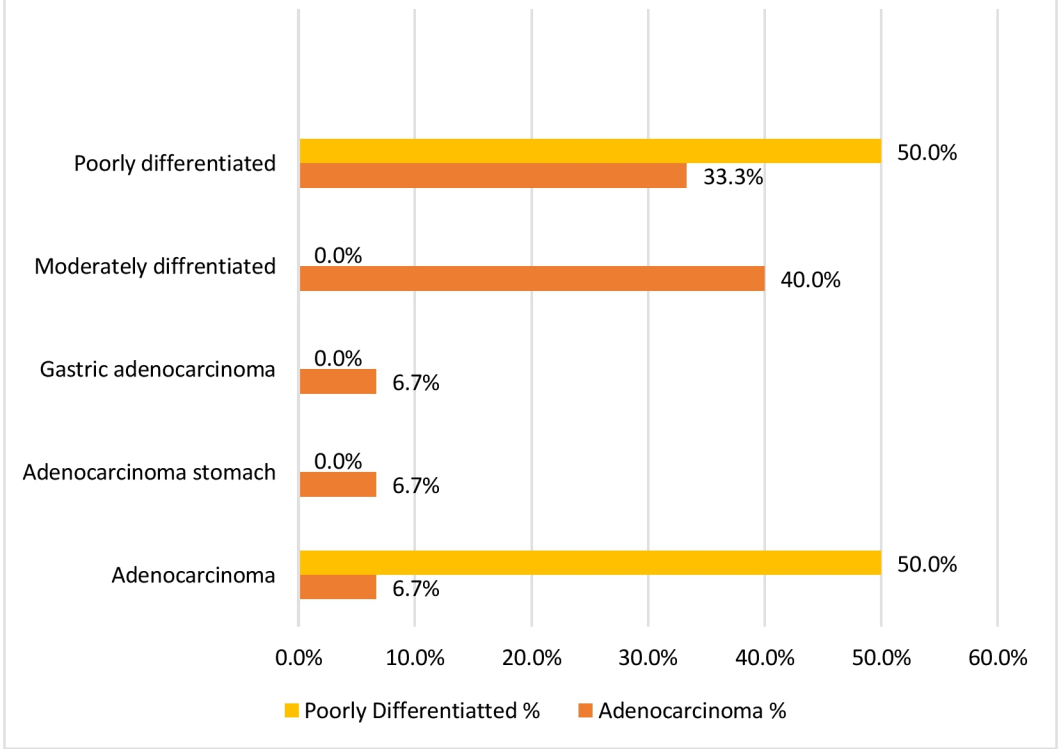
Differentiated	Histopathology			
	Adenocarcinoma		Poorly differentiated	
	N	%	N	%
Adenocarcinoma	1	6. 7%	1	50. 0%
Adenocarcinoma stomach	1	6. 7%	0	0. 0%
Gastric adenocarcinoma	1	6. 7%	0	0. 0%
Moderately differentiated	6	40. 0%	0	0. 0%

Poorly differentiated	5	33. 3%	1	50. 0%
Total	14		2	

Table 15: Association of Histopathology and differentiated in stomach carcinoma cases S

*fisher exact test

The table displays the histopathological differentiation of adenocarcinoma cases, categorizing them as either adenocarcinoma or poorly differentiated. Moderately differentiated adenocarcinoma constitutes the highest proportion at 40. 0%, followed by poorly differentiated adenocarcinoma at 33. 3%. Adenocarcinoma stomach and gastric adenocarcinoma each represent 6. 7% of cases. Poorly differentiated cases have a notably higher percentage within the poorly differentiated category at 50. 0%

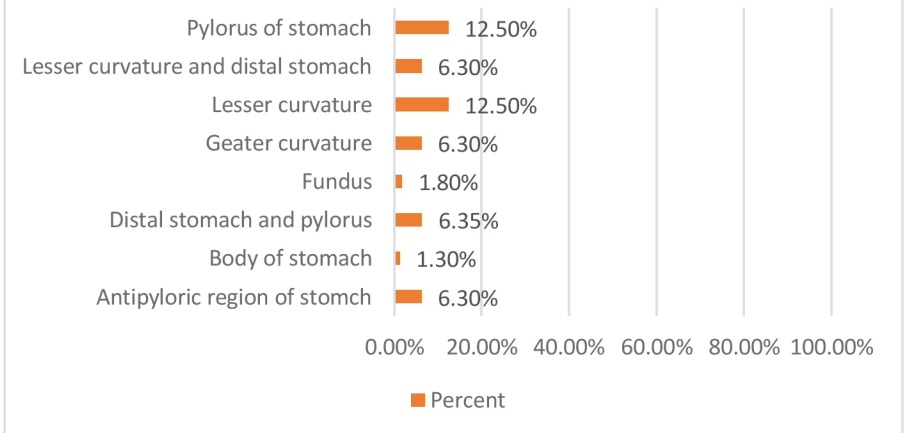


Graph 13

Area of Tumor	Frequency	Percent
Anti-pyloric region of stomach	1	6. 3
Body of stomach	5	31. 3
Distal stomach and pylorus	1	6. 3
Fundus	3	18. 8
Geater curvature	1	6. 3
Lesser curvature	2	12. 5
Lesser curvature and distal stomach	1	6. 3
Pylorus of stomach	2	12. 5
Total	16	100. 0

Table 16: Frequency table of Area of tumor

The table outlines tumor distribution within the stomach, with the body being the most common site at 31. 3%, followed by the fundus at 18. 8%. Other areas include the pylorus, greater curvature, and lesser curvature. Each site's frequency is detailed, contributing to a total of 16 cases.

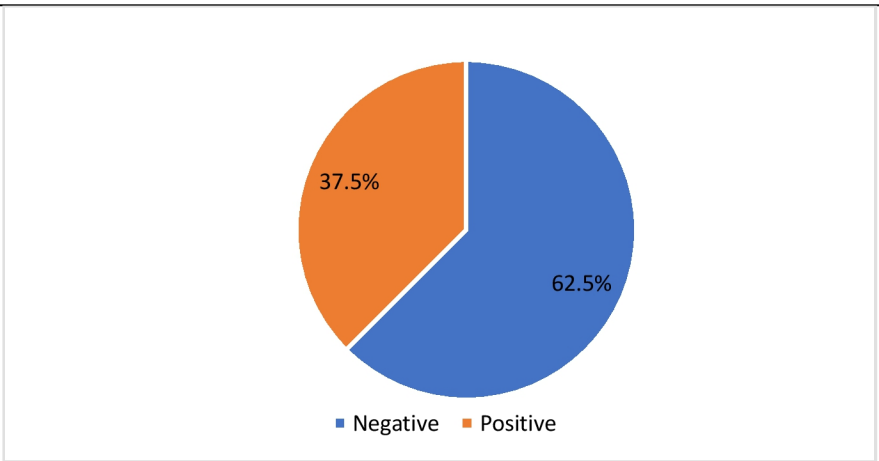


Graph 14

EBV	Frequency	Percent
Negative	10	62. 5%
Positive	6	37. 5%
Total	16	10000. 0%

Table 17: Details of EBV out come

In the dataset, 62. 5% of cases tested negative for Epstein-Barr Virus (EBV), while 37. 5% tested positive. This breakdown illustrates the prevalence of EBV within the sample, with 16 cases contributing to the total, each representing a distinct EBV status.

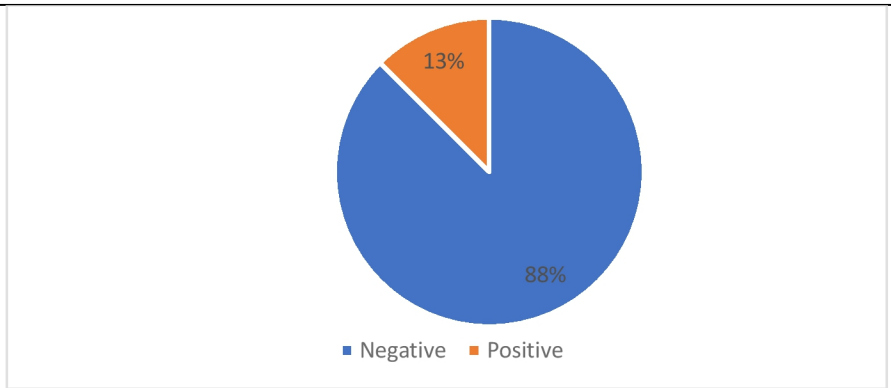


Graph 15

HPV	Frequency	Percent
Negative	14	88%
Positive	2	13%
Total	16	100%

Table 18: Details HPV out come

Among the total cases, 88% tested negative for Human Papillomavirus (HPV), while 13% tested positive. The table provides insight into the prevalence of HPV within the sample, with 16 cases contributing to the total, each representing a distinct HPV status.

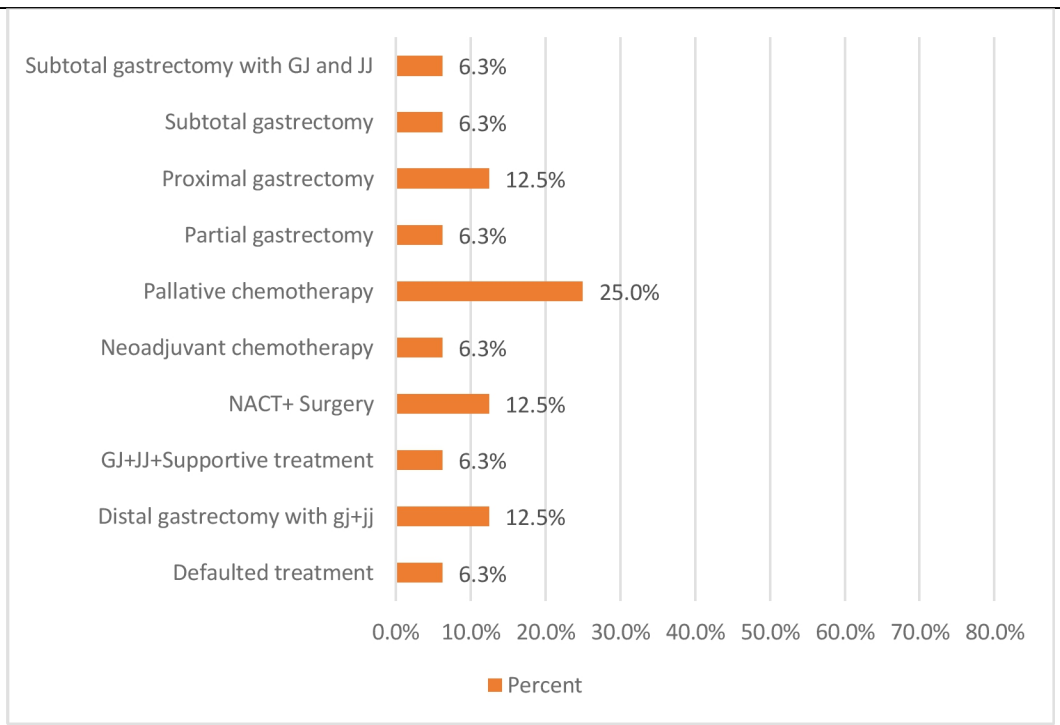


Graph 16

Mode of Treatment	Frequency	Percent
Defaulted treatment	1	6. 3%
Distal gastrectomy with GJ + JJ	2	12. 5%
GJ + JJ + Supportive treatment	1	6. 3%
NACT+ Surgery	2	12. 5%
Neoadjuvant chemotherapy	1	6. 3%
Palliative chemotherapy	4	25. 0%
Partial gastrectomy	1	6. 3%
Proximal gastrectomy	2	12. 5%
Subtotal gastrectomy	1	6. 3%
Subtotal gastrectomy with GJ and JJ	1	6. 3%
Total	16	

Table 19: Frequency table of Mode of treatment to Stomach carcinoma cases

The table delineates the mode of treatment for gastric-related conditions. Palliative chemotherapy constitutes the most prevalent treatment at 25. 0%, followed by various surgical interventions such as proximal and distal gastrectomy, subtotal gastrectomy, and neoadjuvant chemotherapy. Each treatment modality's frequency and percentage contribution to the total of 16 cases are specified, offering insights into therapeutic strategies employed for gastric conditions



Graph 17

No of Nodes Positive	No. of Nodes Retrieved								Total
	0	10	12	19	20	21	31	32	
0	1	1	0	0	0	0	1	0	3
1	0	0	0	1	0	0	0	0	1

4	0	0	0	0	1	0	0	0	1
5	0	0	0	0	0	1	0	0	1
6	0	0	1	0	0	0	0	0	1
21	0	0	0	0	0	0	0	1	1
	1	1	1	1	1	1	1	1	8

Table 20: Association between Number of Node Retrieved and No. of node positive

The table 20 depicts data on the number of positive nodes retrieved against the total number of nodes retrieved in various scenarios. Each row corresponds to a specific scenario

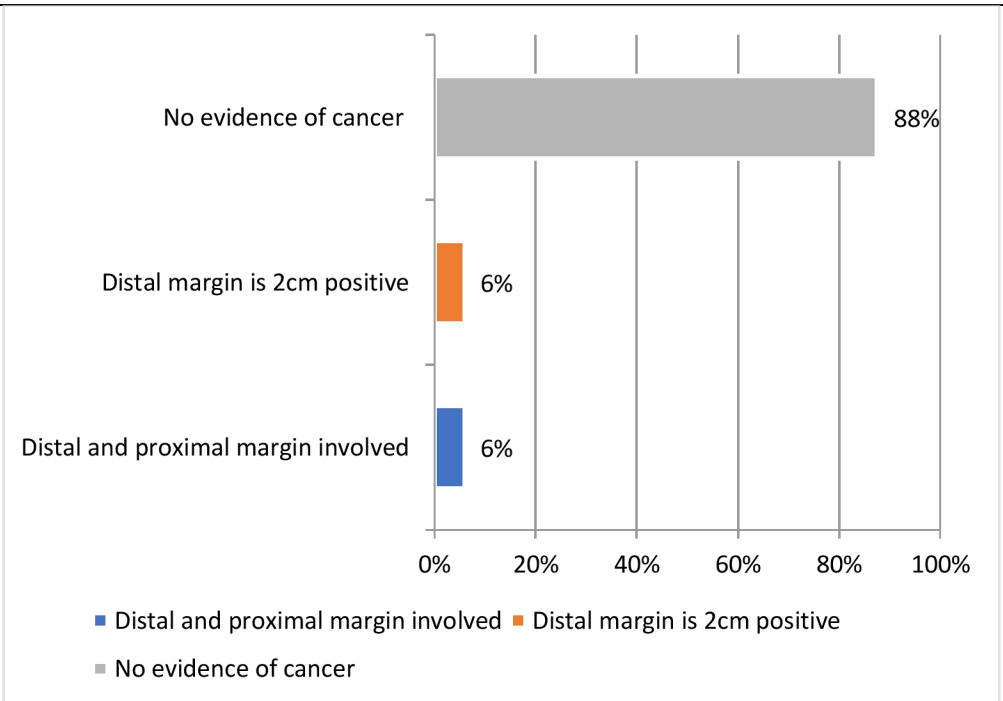
based on the number of nodes retrieved, ranging from 10 to 32 and 0. The subsequent rows represent the number of positive nodes found in each scenario.

- For nodes retrieved, 0 was positive.
- For 10 nodes retrieved, 0 was positive.
- For 12 nodes retrieved, 6 were positive.
- For 19 nodes retrieved, 1 was positive.
- For 20 nodes retrieved, 4 was positive.
- For31 nodes retrieved, 0 were positive.
- For 32 nodes retrieved, 21 were positive.

Margins Positive	**Frequency**	**Percent**
Distal and proximal margin involved	1	6%
The distal margin is 2cm positive	1	6%
No evidence of cancer	14	88%
Total	16	100%

Table 21: Frequency table of Margines Positive

Among 16 cases, 75% showed no evidence of cancer, while 13% had no margin involvement. Distal and proximal margin involvement each accounted for 6% of cases, with one case exhibiting a positive distal margin of 2cm.



Graph 18

BOTH CARCINOMA COMBINED

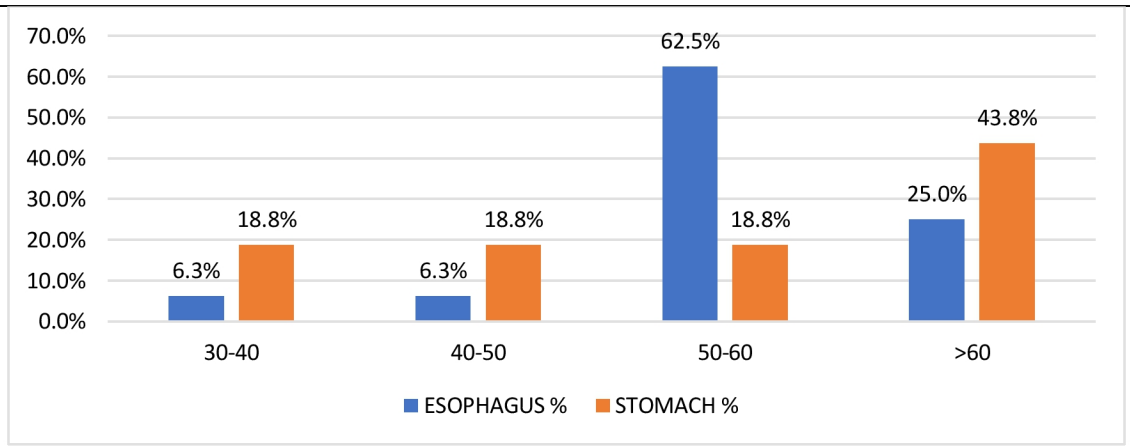
	Type of Carcinoma				Total
Age	Esophagus		Stomach		
	N	%.	N	%	
30-40	1	6. 3%	3	18. 8%	4
40-50	1	6. 3%	3	18. 8%	4

50-60	10	62. 5%	3	18. 8%	13
>60	4	25. 0%	7	43. 8%	11
	16	100. 0%	16	100. 0%	32

Table 22: Details of Age Group and Type of Carcinoma

*fisher exact test (P- value 0. 086)

Table 22 reveals that out of the total patients of Exophages carcinoma highest patients were observed in the age group 50-60 years (62. 5%). While the highest patients in Stomach carcinoma were observed in more than 60 years (43. 8%). Age was not significantly associated with type of cancer. (P- value 0. 086)



Graph 19

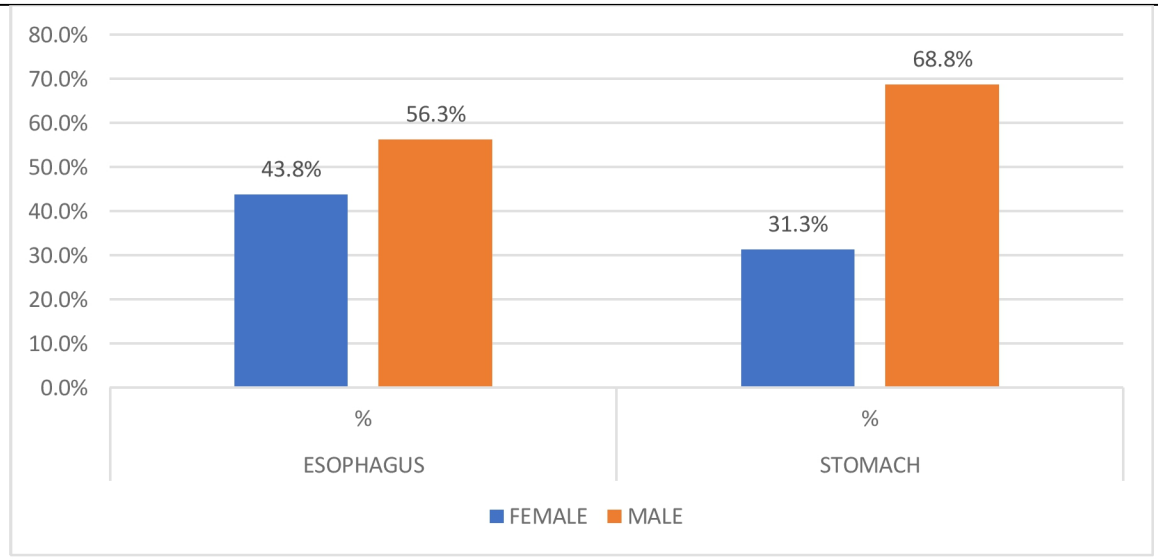
	Type of Carcinoma				**Total**
Sex	**Esophagus**		**Stomach**		
	N	%	N	%	
Female	7	43. 8%	5	31. 3%	12
Male	9	56. 3%	11	68. 8%	20

	16	100. 0%	16	100. 0%	32

Table 23: Details of Gender and Type of Carcinoma

*Chi Square test (P-value 0. 465)

Table 23 reveals that males were predominant among the total patients with esophageal carcinoma (62. 5%) and stomach carcinoma (68. 8%), but this difference is not statistically significant (P-value 0. 465).

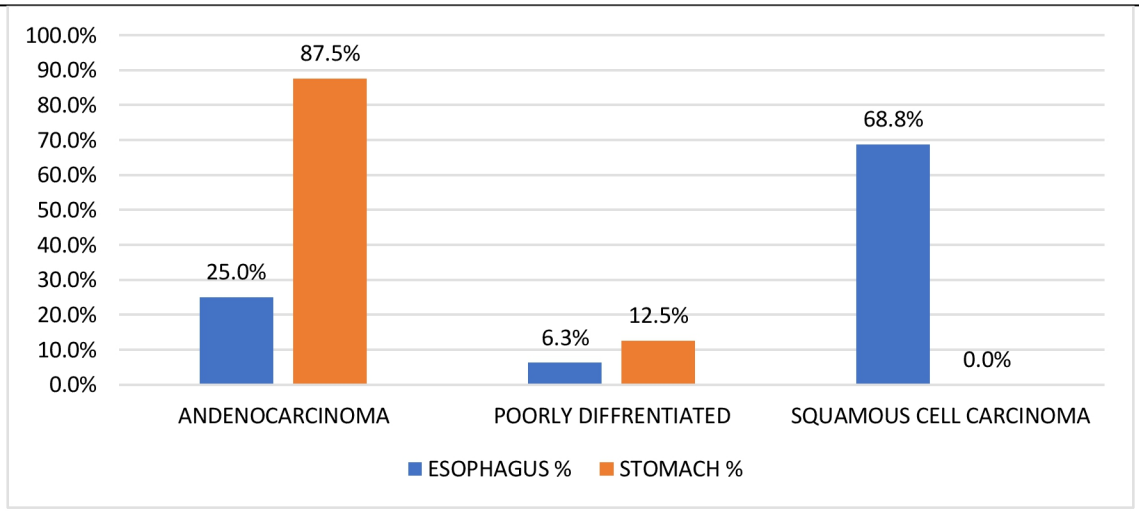


Graph 20

	Type of Carcinoma				Total
Histopathology	**Esophagus**		**Stomach**		
	N	%	N	%	
Adenocarcinoma	4	25. 0%	14	87. 5%	18
Poorly Differentiated	1	6. 3%	2	12. 5%	3
Squamous Cell Carcinoma	11	68. 8%	0	0. 0%	11
	16	100. 0%	16	100. 0%	32

Table 24: Details of Histopathology and type of Carcinoma
*Fisher Exact test (P<0. 001)

Table 24 depicts the details of histopathology and type of carcinoma. Among the total cases of esophageal carcinoma, 68. 8% were diagnosed with squamous cell carcinoma, whereas no patients with stomach carcinoma were found to have squamous cell carcinoma. In stomach carcinoma, adenocarcinoma was observed in the highest percentage (87. 5%). Histopathology, specifically adenocarcinoma, is significantly associated with stomach carcinoma (P < 0. 001).



Graph 21

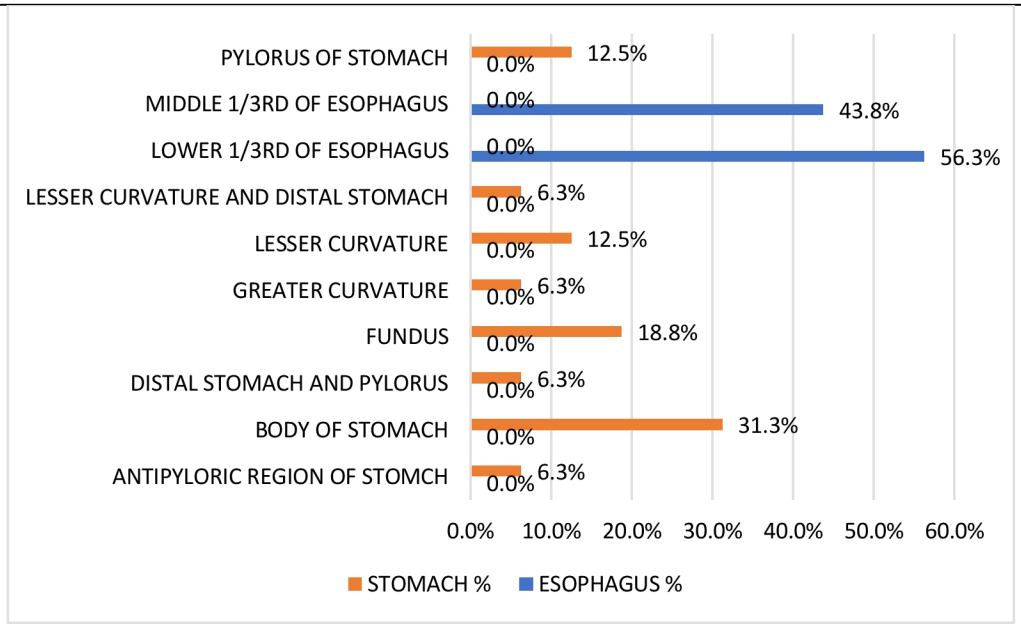
	Type of Carcinoma				**Total**
Area of Tumour	**Esophagus**		**Stomach**		
	N	%	N	%	
Anti-pyloric Region of Stomach	0	0. 0%	1	6. 3%	1
Body of Stomach	0	0. 0%	5	31. 3%	5
Distal Stomach and Pylorus	0	0. 0%	1	6. 3%	1

Fundus	0	0. 0%	3	18. 8%	3
Greater Curvature	0	0. 0%	1	6. 3%	1
Lesser Curvature	0	0. 0%	2	12. 5%	2
Lesser Curvature and Distal Stomach	0	0. 0%	1	6. 3%	1
Lower 1/3rd of Esophagus	9	56. 3%	0	0. 0%	9
Middle 1/3rd of Esophagus	7	43. 8%	0	0. 0%	7
Pylorus of Stomach	0	0. 0%	2	12. 5%	2
Total	16	100. 0%	16	100. 0%	32

Table 25: The distribution of carcinoma types by tumor location for esophageal and stomach cancers

*Fisher exact test (P <0. 0001)

Table 25 illustrates the distribution of tumor locations for esophageal and stomach carcinoma cases. In esophageal carcinoma, most tumors were found in the lower third (56. 3%) and the middle third (43. 8%) of the esophagus. Conversely, stomach carcinoma tumors were more dispersed across various regions. The body of the stomach was the most common site (31. 3%), followed by the fundus (18. 8%) and the lesser curvature (12. 5%). Tumors were also present in the antrum and pylorus regions, each accounting for 6. 3%, and the greater curvature, lesser curvature and distal stomach, and the pylorus of the stomach each contributing to the total cases. Notably, there were no squamous cell carcinomas in the stomach; adenocarcinoma predominated in stomach cancer cases (87. 5%) his distribution underscores the regional preferences of different carcinoma types and highlights the significant association of adenocarcinoma with stomach carcinoma (P < 0. 001).



Graph 22

	Type of Carcinoma				Total
Stage	**Esophagus**		**Stomach**		
	N	**%**	**N**	**%**	
-	9	56. 3%	7	43. 8%	16
pT2N0Mx	0	0. 0%	1	6. 3%	1
pT2N0MX-IIIB	0	0. 0%	1	6. 3%	1
pT3aN2Mx	0	0. 0%	1	6. 3%	1
pT3N1MX-IIB	0	0. 0%	1	6. 3%	1
PT4AN2BMX-IIIA	0	0. 0%	1	6. 3%	1
pT4aN3aMx	0	0. 0%	1	6. 3%	1
pyT1BN2MX-III	1	6. 3%	0	0. 0%	1
T3N3MX-IVA	1	6. 3%	0	0. 0%	1
YpT1AN3MX-IVA	1	6. 3%	0	0. 0%	1
ypT1BN0MX	1	6. 3%	0	0. 0%	1

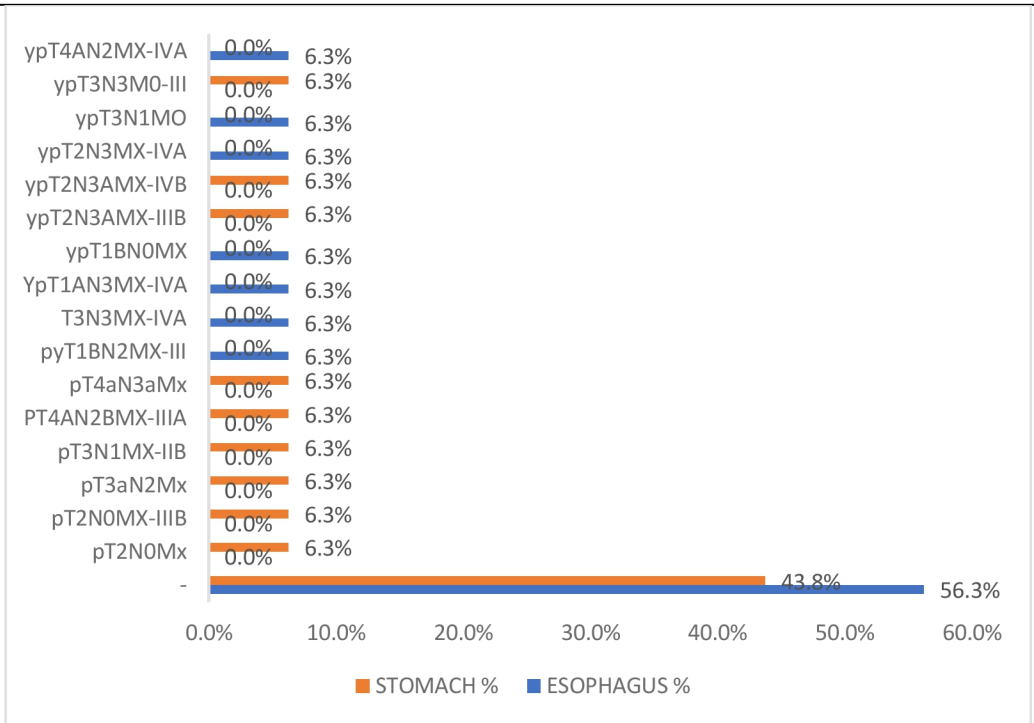
ypT2N3AMX-IIIB	0	0. 0%	1	6. 3%	1
ypT2N3AMX-IVB	0	0. 0%	1	6. 3%	1
ypT2N3MX-IVA	1	6. 3%	0	0. 0%	1
ypT3N1MO	1	6. 3%	0	0. 0%	1
ypT3N3M0-III	0	0. 0%	1	6. 3%	1
ypT4AN2MX-IVA	1	6. 3%	0	0. 0%	1
	16	100. 0%	16	100. 0%	32

Table 26

(Note: - statistical test cannot apply due to small sample size and more classification)

Table 26 Shows the staging of esophageal and stomach carcinoma cases. Among the 16 oesophageal carcinoma cases, 56. 3% (9 cases) were unspecified for stage. The remaining cases were distributed across various stages: pT1BN2MX-III (6. 3%), T3N3MX-IVA (6. 3%), YpT1AN3MX-IVA (6. 3%), ypT1BN0MX (6. 3%), ypT2N3MX-IVA (6. 3%), ypT3N1M0 (6. 3%), and ypT4AN2MX-IVA (6. 3%).

In contrast, the 16 stomach carcinoma cases showed a more diverse distribution: 43. 8% were unspecified for stage. The remaining cases included pT2N0Mx (6. 3%), pT2N0MX-IIIB (6. 3%), pT3aN2Mx (6. 3%), pT3N1MX-IIB (6. 3%), PT4AN2BMX-IIIA (6. 3%), pT4aN3aMx (6. 3%), ypT2N3AMX-IIIB (6. 3%), ypT2N3AMX-IVB (6. 3%), ypT3N3M0-III (6. 3%).



Graph 23

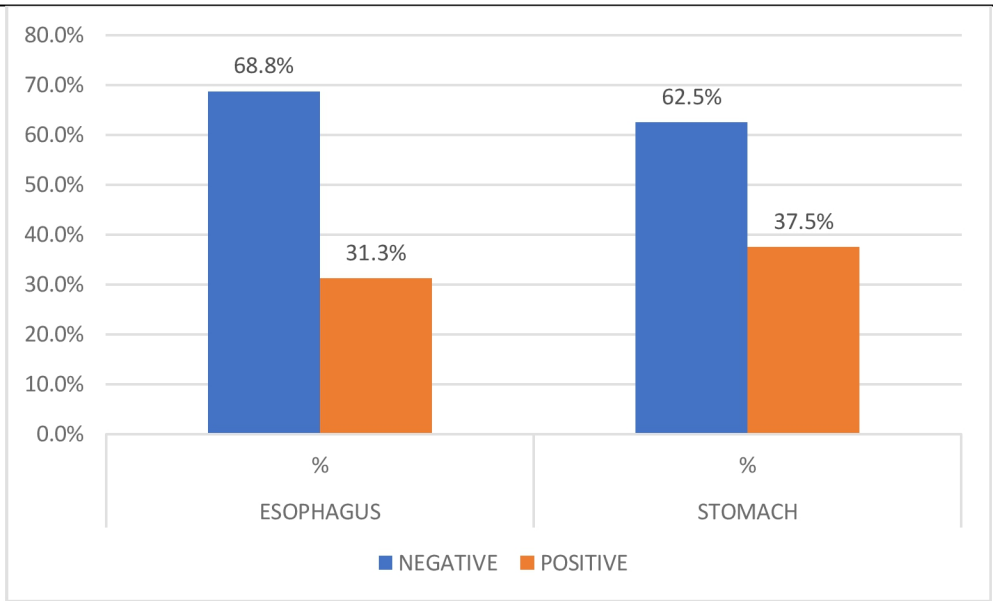
	Type of Carcinoma				Total
EBV	**Esophagus**		**Stomach**		
	N	%	N	%	
Negative	11	68. 8%	10	62. 5%	21
Positive	5	31. 3%	6	37. 5%	11
	16	100. 0%	16	100. 0%	32

Table 27: The Association between EBV and Type of Carcinoma

Chi Square test (P- value >0. 7097)

Table 27 presents the distribution of Epstein-Barr Virus (EBV) status among patients

with esophageal and stomach carcinomas. Out of 16 esophageal carcinoma cases, 68. 8% (11 cases) were EBV-negative, and 31. 3% (5 cases) were EBV-positive. Similarly, among the 16 stomach carcinoma cases, 62. 5% (10 cases) were EBV-negative, and 37. 5% (6 cases) were EBV-positive. In total, 21 cases (65. 6%) were EBV-negative, and 11 cases (34. 4%) were EBV-positive out of the 32 cases studied. Type of Carcinoma is not statistically significant. (P-Value >0. 7097)



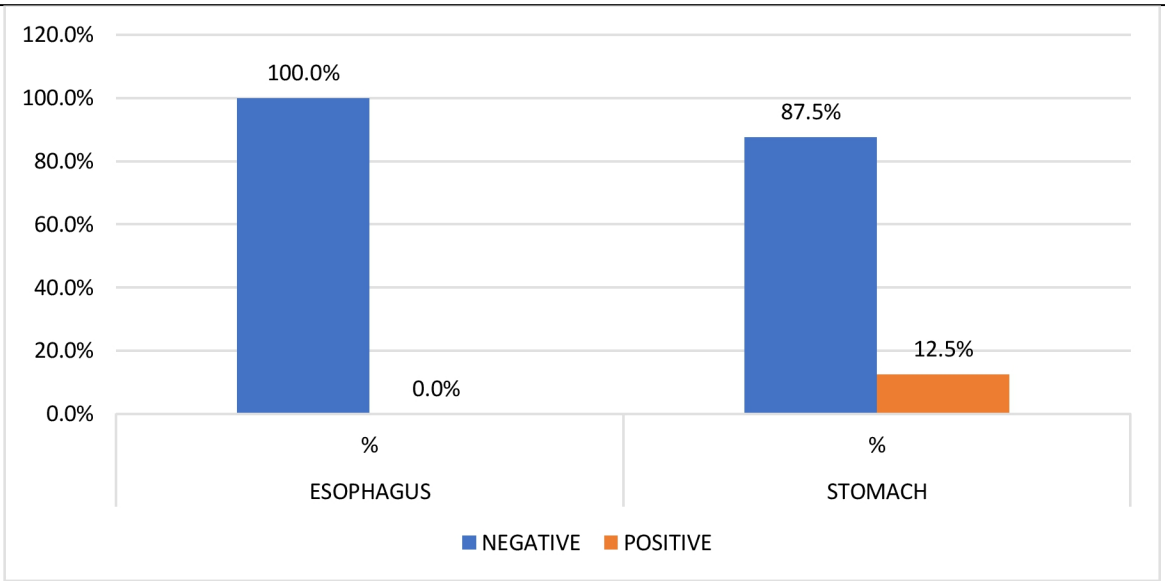
Graph 24

	Type of Carcinoma				Total
HPV	**Esophagus**		**Stomach**		
	N	%	N	%	
Negative	16	100%	14	87. 5%	30
Positive	0	0%	2	12. 5%	2
	16	100%	16	100. 0%	32

Table 28: The Association between HPV and Type of Carcinoma

*Chi square test (P- Value 0. 144)

Table 28 presents the Human Papillomavirus (HPV) status among patients with esophageal and stomach carcinomas. All 16 oesophageal carcinoma cases (100%) were HPV-negative. Among the 16 stomach carcinoma cases, 87. 5% (14 cases) were HPV-negative, and 12. 5% (2 cases) were HPV-positive. Overall, out of the 32 cases studied, 30 cases (93. 8%) were HPV-negative, and 2 cases (6. 3%) were HPV-positive. There were no statistically significant association between EBV and Type of carcinoma. (P-Value 0. 144)



Graph 25

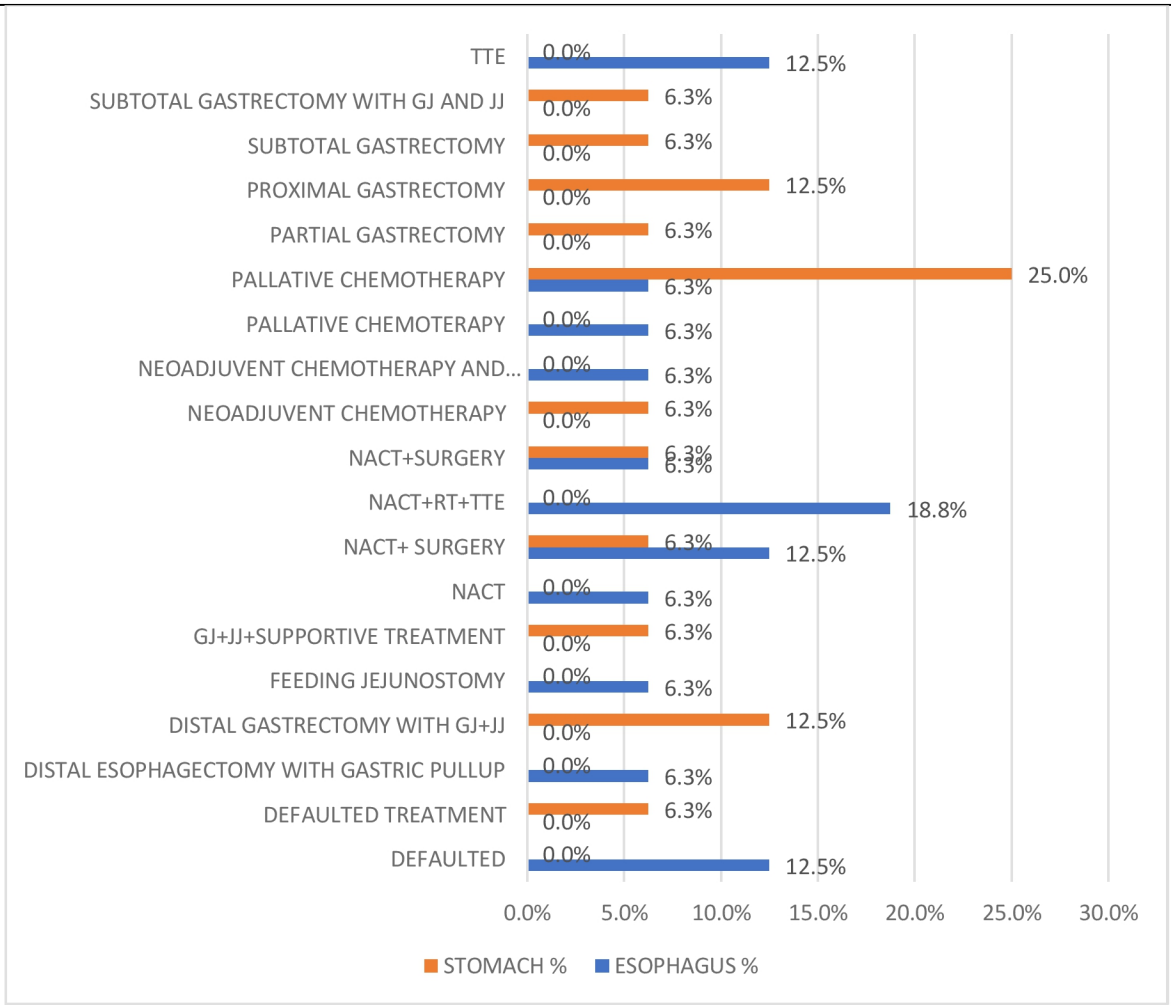
Mode	Type of Carcinoma		Treatment		Total
	Of				
	N	%	N	%	
Defaulted	2	12. 5%	0	0. 0%	2
Defaulted Treatment	0	0. 0%	1	6. 3%	1

Distal Esophagectomy with Gastric Pullup	1	6. 3%	0	0. 0%	1
Distal Gastrectomy with GJ+JJ	0	0. 0%	2	12. 5%	2
Feeding Jejunostomy	1	6. 3%	0	0. 0%	1
GJ + JJ+ Supportive Treatment	0	0. 0%	1	6. 3%	1
NACT	1	6. 3%	0	0. 0%	1
NACT+ Surgery	2	12. 5%	1	6. 3%	3
NACT+RT+TTE	3	18. 8%	0	0. 0%	3
NACT + Surgery	1	6. 3%	1	6. 3%	2
Neoadjuvant Chemotherapy	0	0. 0%	1	6. 3%	1
Neoadjuvant Chemotherapy and Radiotherapy	1	6. 3%	0	0. 0%	1
Palliative Chemotherapy	1	6. 3%	0	0. 0%	1
Palliative Chemotherapy	1	6. 3%	4	25. 0%	5
Partial Gastrectomy	0	0. 0%	1	6. 3%	1
Proximal Gastrectomy	0	0. 0%	2	12. 5%	2
Subtotal Gastrectomy	0	0. 0%	1	6. 3%	1
Subtotal Gastrectomy with GJ and JJ	0	0. 0%	1	6. 3%	1
TTE	2	12. 5%	0	0. 0%	2
	16	100. 0%	16	100. 0%	32

Table 29: The distribution of treatment modalities based on the type of carcinoma

Table 8 presents the distribution of treatment modalities based on the type of carcinoma. The most common treatment for defaulted patients was no treatment (12. 5%). Notably, palliative chemotherapy was the predominant treatment for stomach carcinoma, representing 25. 0% of cases. Overall, there were 16 cases in each carcinoma category, totaling 32 cases.

This data aids in understanding the prevalent treatment approaches across different carcinoma types, highlighting variations in therapeutic strategies based on tumor location and patient condition.



Graph 26

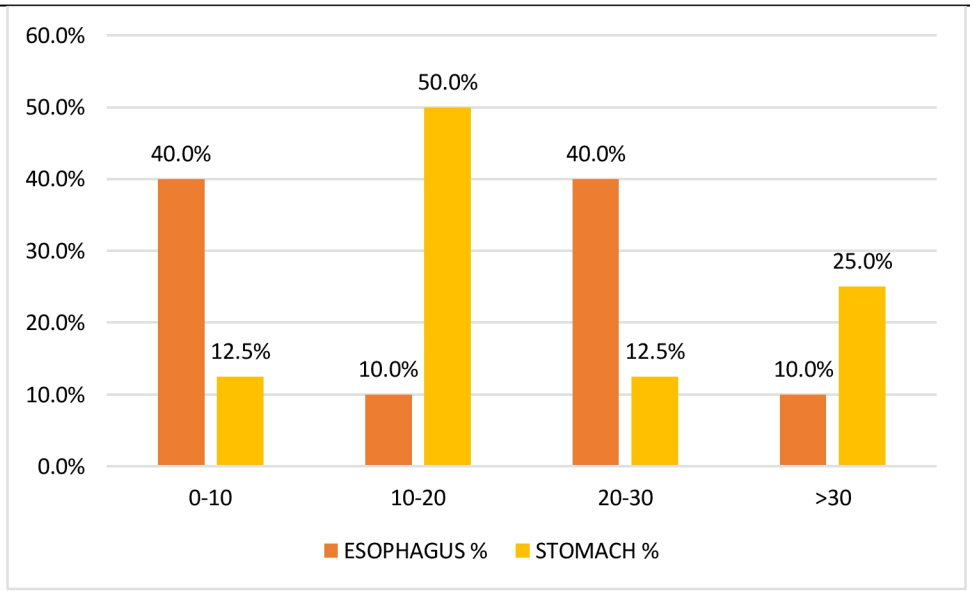
	Type of Carcinoma			
	Esophagus		Stomach	
No of Nodes Retrieved	**N**	**%**	**N**	**%**
0-10	4	40. 0%	1	12. 5%
10-20	1	10. 0%	4	50. 0%

20-30	4	40. 0%	1	12. 5%
>30	1	10. 0%	2	25. 0%
	10		8	

Table 30: Distribution of Number of nodes retrieved and type of carcinoma

*Fisher exact test (P- value 0. 0173)

Table 30 illustrates the distribution of the number of nodes retrieved and types of carcinomas. In esophagus carcinoma, the highest number of nodes retrieved falls within the ranges of 0-10 and 20-30, constituting 40% of the total. Conversely, in stomach carcinoma, the highest number of nodes retrieved lies between 10-20. No of Nodes Retrieved were significantly associated with type of carcinoma. (P- value 0. 0173)



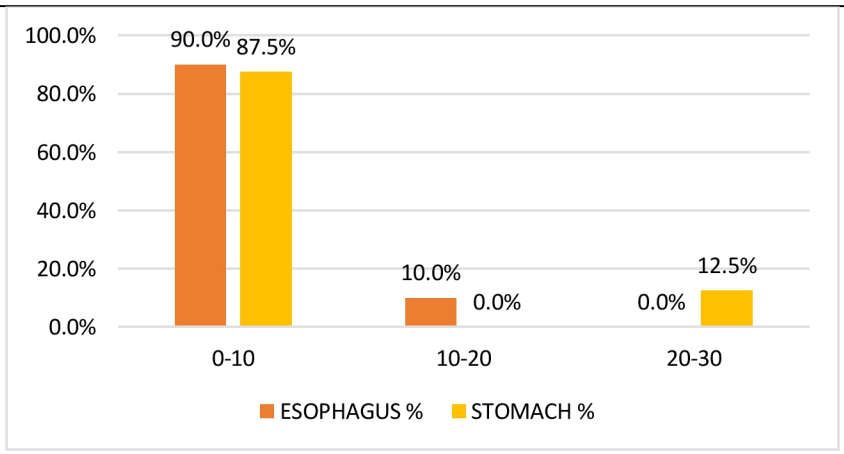
Graph 27

	Esophagus		Stomach	
	N	**%**	**N**	**%**
0-5	4	40. 0%	8	100. 0%
>5	6	60. 0%	0	0. 0%
Total	10	100. 0%	8	100. 0%

Table 31: Distribution of number of nodes positive and type of carcinoma

Fisher Exact test (P- Value 0. 01)

The table presents data on the distribution of a variable in the esophagus and stomach. For the esophagus, 40% (4 out of 10) of cases fall in the 0-5 range, and 60% (6 out of 10) fall in the >5 range. For the stomach, 100% (8 out of 8) of cases fall in the 0-5 range, with no cases in the >5 range. The Fisher Exact test yields a P-value of 0. 01, indicating a statistically significant difference between the distributions in the esophagus and stomach. This suggests that the variable's distribution differs significantly between the two organs.



Graph 28

DISCUSSION

DISCUSSION

In the present study, there were a total of 32 cancer cases. Out of these, 16 (50%) were and 16 (50%) were stomach carcinoma. Out of the total esophagus cases HPV positive was not observed in any case of esophagus carcinoma and HPV positive was found in 2(2. 5%) in gastric cases. EBV was positive in 5 (31. 2%) esophagus and 6 (37. 5%) gastric carcinoma cases.

ESOPHAGEAL CARCINOMA

Among the total 16 patients, males were more prevalent (56. 3%) compared to females (43. 8%). In the 30-40 age group, all 4 patients (44. 4%) were male. The 40-50 age group had only 1 patient, who was female (14. 3%). In the 50-60 age group, there was 1 male patient (11. 1%) and no females. In the >60 age group, females were predominant, with 6 patients (85. 7%), while males constituted 4 patients (44. 4%). This indicates a higher occurrence of esophageal carcinoma in older females and younger males.

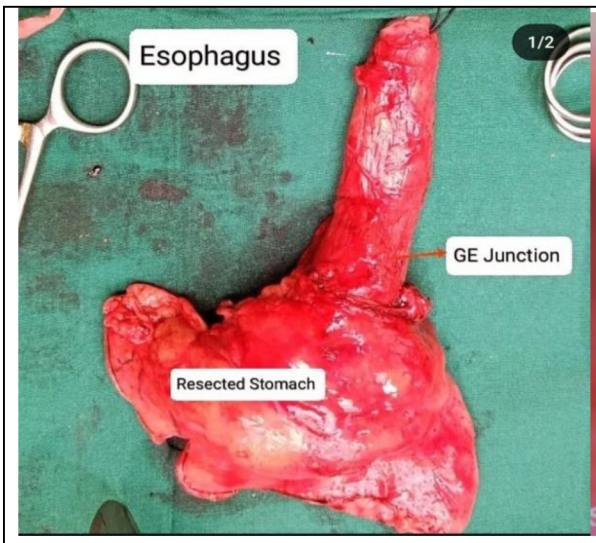


Figure 5: Intra operative picture of Carcinoma Esophagus

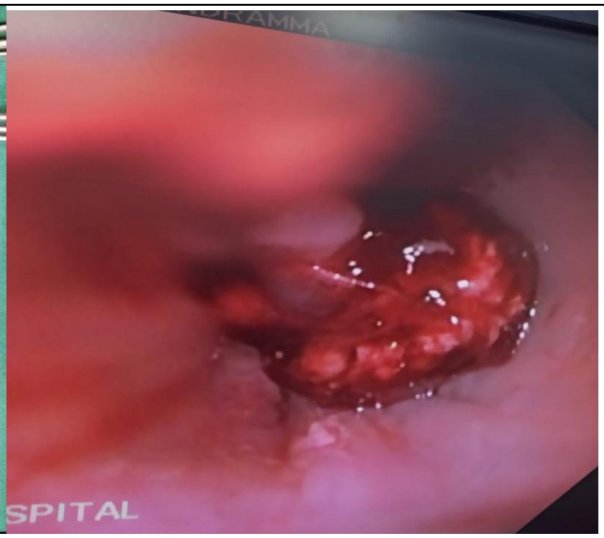


Figure 6: Endoscopic Picture of Carcinoma Esophagus Resected with Part of Stomach

The average age group, according to retrospective data from 552 patients examined over a 20-year period by Choksi D et al,[65] is 54.78 years. According to population-based data, esophageal cancer incidence peaks in many parts of the world around the sixth decade, which was comparable to.[66] In our analysis, this is a decade earlier than some of the western evidence.[67] The mean age in a recent Indian study was 51. 7 years.[68] In our study, the male to female ratio was 1. 6 and 1. 72. In the previously described study, this was 2. 53.[68] Furthermore, all major cancer registries in India have low sex ratios, with a national average of 1.:2.[69] According to WHO data, the incidence of carcinoma esophagus is two to three times higher in men than in women (male to female ratio: 2.4). In a similar vein, a recent African study revealed a majority of men.[70] Thus, the findings of our investigation support the gender ratio for esophageal cancer in India. It is necessary to determine the cause of India's higher frequency among females. The high rate of tobacco use in any form among Indian women could be the cause of this.[71] Nevertheless, our results diverge from a study conducted by Wang et al., which demonstrated that incidence is rising among females in a small number of nations.[72]

One type of cancer that typically affects men three to four times more frequently than women is esophageal cancer. Cancer can be classified into two main types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC).[73] The primary risk factors for ESCC are aging, male sex, alcohol use, and cigarette smoking; the primary risk factors for EAC are gender, cigarette smoking, obesity, and gastroesophageal reflux illness (which can cause Barret's dysplasia (BD)).[74-75]

Among the 16 patients with esophagus carcinoma, squamous cell carcinoma was the most common type (68. 8%), followed by adenocarcinoma (25. 0%), and poorly differentiated carcinoma (6. 3%). The majority of cases were either moderately differentiated (37. 5%) or well differentiated (37. 5%). Poorly differentiated carcinomas account for 12. 5% of cases.

Adenocarcinoma and mucinous carcinoma each represent 6. 3% of the total. This distribution indicates that moderately and well-differentiated carcinomas are equally common among the patients, suggesting a relatively balanced differentiation profile. The lower frequencies of poorly differentiated and specific types like adenocarcinoma and mucinous carcinoma highlight their lesser prevalence in this patient group. Overall, the data points to a significant variation in the differentiation status of exophages carcinoma among the patients.

Among adenocarcinoma cases (n=4), 50. 0% were moderately differentiated, 25. 0% were poorly differentiated, and 25. 0% were well differentiated. Squamous cell carcinoma (n=11) was predominantly well differentiated (54. 5), followed by moderately differentiated (36. 4%), and mucinous carcinoma (9. 1%). No mucinous carcinoma or well-differentiated cases were observed in the adenocarcinoma group. This indicates that squamous cell carcinoma shows a higher prevalence of well-differentiated cases, whereas adenocarcinoma exhibits a broader range of differentiation.

80. 25% of the patients had SCC, while 16. 67% had AC, according to Choksi D.[65] The SCC to AC ratio was 5. 15. This outcome is consistent with other Indian research that also report SCC predominance.[76–80] This result differs significantly from a previous retrospective data set that displayed a lower SCC to AC ratio of 3:1 and from a related study that found a ratio of 3.18:1.[81–82] The authors came to the conclusion that, at least in our region of the world, it is doubtful that AC will overtake SCC anytime soon given the high percentage distribution of SCC (80. 25%) over AC (16.67%). Some possible explanations for the high incidence of SCC include the existence of risk factors such alcohol, tobacco, and smoking usage, a large proportion of patients from lower socioeconomic strata, and dietary inadequacies.

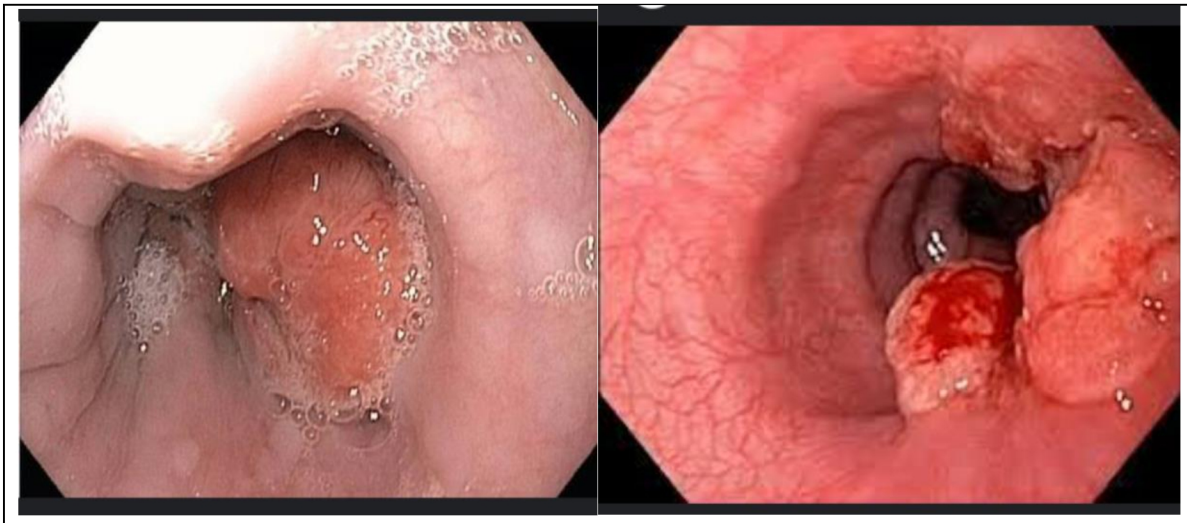


Figure 7: Endoscopic Picture of Carcinoma Lower 1/3rd of Esophagus

HPV and Esophageal Cancer

In our investigation, no positive HPV infections were found in oesophageal instances. Human papillomavirus (HPV) may or may not play a role in the development of esophageal squamous cell carcinoma (ESCC); numerous Chinese studies have already found positive correlations between the two variables, but research from Western nations has generally found no conclusive evidence of such relationships.[83–86] This could indicate that there is no way to rule out HPV DNA contamination as the reason for the high HPV prevalence in ESCC tissue.[85] A robust correlation between high-risk HPV and both BD and EAC was demonstrated by Rajendra et al. 81 patients out of 261 were positive for HPV DNA. In both the BE and the controls, HPV was primarily found at the transition zone. In BD (68. 6%, incidence rate ratio (IRR) 2. 94, 95% confidence interval (CI) 1. 78–4. 85, $p < 0.001$) and EAC (66. 7%, IRR 2. 87, 95% CI 1. 69–4. 86, $p < 0.001$), HPV positive was substantially more prevalent than in controls (18. 0%).[87] They investigated whether there was a noticeable genetic difference between HPV-positive and HPV-negative EAC based on the study's findings. In comparison to the patients with esophageal cancer who were virus-negative, the HPV-positive cohort had almost 50% fewer non-silent somatic mutations (1. 31 mutations/Mb vs. 2. 56 mutations/Mb,

p = 0. 048). In terms of TP53 aberrations, 50% of the HPV-negative EAC patients tended to have TP53 mutations, but they were absent in the HPV-positive EAC group. The findings point to distinct biological pathways for the development of tumors in HPV-positive and HPV-negative EAC.[88] Agalliu et al.'s study found no correlation between the risk of esophageal cancer and HPV16 or any other oral alpha, beta, or gamma HPVs.[89] While there is proof of a considerable correlation between EAC and high-risk HPVs, the relationship between ESCC and HPV still must be further investigated.

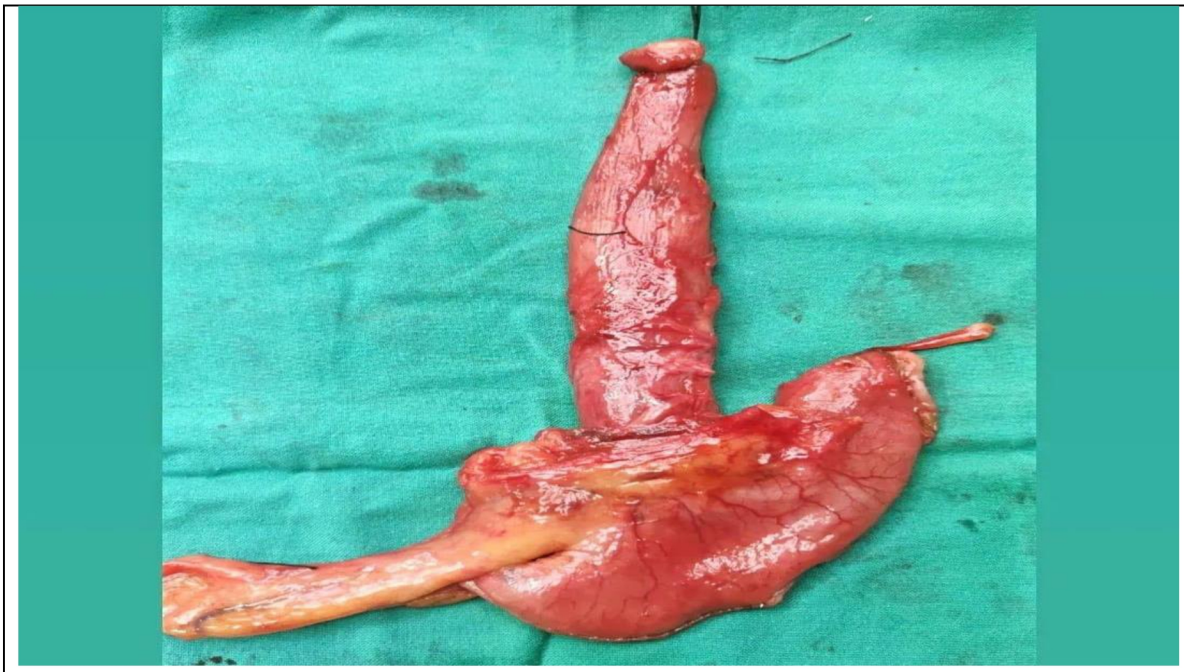


Figure 8: Carcinoma esophagus who has proved positive for HPV in Testing

According to Petrelli et al., HPV is found in about 1 in 5 ESCC patients, with varying regional prevalence.[90] In light of these regional variations, Asia has a notably high HPV prevalence in esophageal cancer.[90–91] It is unclear exactly how HPV causes normal squamous cells to change into cancerous cells, however oncogenic HPV E6 and E7 genes increase the pathogenesis of ESCC by upregulating susceptible human leukocyte antigen-DQB1 through DNA demethylation.[92] Only a few publications have connected HPV infection to Barrett's esophagus and EAC, and some instances are HPV-negative.[93] Using fresh frozen tissue,

Rajendra et al. claim that anomalies in the wild-type p53 and retinoblastoma protein pathways characterize the active involvement of HPV in Barrett's dysplasia and EAC.[94] More research is required, involving a large number of cases and accounting for the regional differences between the EAC and ESCC.

HPV and ESCC

Recent meta-analyses and studies indicate that the global frequencies of HPV-ESCC infection vary from 11.7% to 38.9%. [95–97] According to Syrjänen et al,[98] the range of HPV prevalence was 0% to 78%, with a mean of 29.0%. The greatest predictor of the observed differences in infection rates was geographic origin. High-incidence nations like China and Iran had ESCC rates as high as 250 per 100,000 people, but low-incidence nations like the United States and Australia had ESCC rates of about 2.5 per 100,000 people. [99-103] For the most part, this unequal regional distribution is yet unknown. Variability in HPV-ESCC infection rates has been linked to HPV detection techniques in several studies. Various methods were employed to uncover proof of HPV's connection to ESCC.[102] The majority of research employ both ISH and PCR, which are now the most widely utilized methodologies. Depending on the technique of detection, the overall prevalence of HPV infection varies greatly. The prevalence of infection varied from 17.6% for Southern blots to 32.2% for L1 serology; nevertheless, the two most widely used techniques showed comparable overall rates of HPV-ESCC, at 27.7% and 24.3%, respectively.[100] Together with these research, a number of meta-analyses have shown that the heterogeneity observed in reported HPV-ESCC infection rates cannot be explained by the detection method alone, as variability is present even among studies using the same technology.[103] It was first proposed in 1982 by Syrjänen et al. [104] and Syrjänen [105] that HPV may be a contributing factor in the development of esophageal squamous cell carcinoma, both benign and malignant.

The established correlation between HPV and oropharyngeal SCC, along with the

histologic similarities between the upper esophagus and oral squamous epithelium, may indicate a similar relationship. Numerous research has been carried out on this subject in a number of nations, including Australia, China, Korea, Iran, India, and the United States. [106-107] Seventy percent of instances of cervical cancer are believed to be connected to HPV 16 and HPV 18, which are the most commonly found strains in HPV-associated malignancies. A strong correlation was shown by Yong et al,[96] between HPV16 and ESCC, but not between HPV18 and ESCC. An overall HPV16 prevalence rate of 11. 7% was reported in this meta-analysis, compared to 1. 8% for HPV18. Additionally, they computed distinct odds ratios (ORs) for HPV16 (OR = 3.55) and HPV18 (OR = 1.25), revealing that HPV16 was the most detected subtype in ESCC. This result was consistent with recent systematic reviews that demonstrated HPV16 was the strain most frequently found in HPV-ESCC infections by a variety of techniques. However, research on the possible aetiological significance of HPV infection in ESCC has yielded conflicting results thus far. There is minimal to no correlation between p16 overexpression and HPV positivity in the numerous investigations of HPV infection in ESCC. According to a recent systematic study, the odds ratio of HPV-positivity in an ESCC lesion with overexpression of p16 was 1. 07 (95%CI: 0. 70-1. 62), indicating that p16 is not a reliable predictor of HPV status in ESCC.[108] P16 overexpression has not been assessed in recent meta-analyses to describe the possible aetiological function of HPV infection in ESCC. Research looking at p16 overexpression and HPV positivity in ESCC has found that only about 5% of cases have double-positive ESCC lesions. [109–110] Since the current data differ significantly from those on oropharyngeal and cervical cancer, there is still no evidence linking p16 to HPV in ESCC. Taken together, p16-overexpression and HPV serological data seem to suggest that HPV may not be a major oncogene in ESCC, even with reported rates of HPV infection. However, it would be remarkable if there was no association between p16-overexpression and HPV oncoactivity in ESCC.[111]

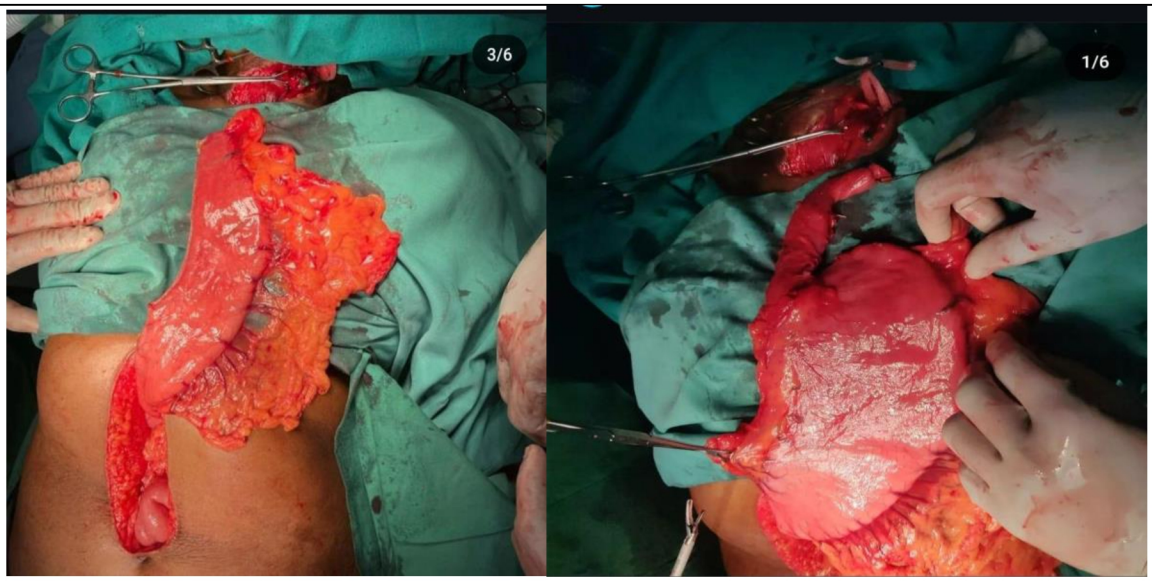


Figure 9: Thoracic Esophagectomy with Gastric Pull-up procedure through thoracoabdominal approach

There may be a causative connection between HPV and ESCC based on their geographic association. Studies from the same geographic regions reveal wide variations in HPV-ESCC infection rates, therefore this correlation needs to be interpreted cautiously.[112] As a result, the part HPV plays in ESCC is yet unclear. The interpretation of current studies is complicated by geographic variety and methodological heterogeneity, resulting in inconsistent conclusions.

Although there is a clear correlation between HPV prevalence and high-ESCC incidence locations, HPV-ESCC infection rates are low (between 5% and 15%) in Western nations like the United States. HPV serological findings and p16 overexpression do not presently support a conclusive HPV etiological role in ESCC. HPV and EAC: In the West, EAC is one of the tumors that is developing the quickest.[113] HPV may potentially be involved in EAC, as evidenced by the same increase in head and neck malignancies in Western nations. Warty (papillomatous) lesions in the esophagus have frequently been observed by endoscopists

and pathologists; these lesions may be indicative of a viral infection.[114]

For the first time, Rajendra et al.'s recent study [87] revealed a high correlation between transcriptionally active hr-HPV and Barrett's dysplasia (BD) and EAC, although HPV was not physiologically significant in BE. This study was the first to discover that patients with BD and EAC had much greater levels of HPV positive, as determined by PCR, than did controls and people with Barrett's metaplasia. This study implied that HPV was linked to the change from BE to dysplastic disease/adenocarcinoma, even though it was unable to establish causation. The goal of studying biomarkers associated with hr-HPV transcriptional activity is to pinpoint the high-risk subset of cancer progressors. [115-116] Along the Barrett's metaplasia-dysplasia-adenocarcinoma sequence, there was a very substantial correlation between the severity of the disease and positive results for HPV DNA and markers of viral transcriptional activity, such as p16 and E6/E7 mRNA, as opposed to negative results for all markers. In the Barrett's metaplasia-dysplasia-adenocarcinoma pathway, there was a substantial correlation between the severity of the disease and both an increased hr-HPV viral load and integration into the host genome. Another recent prospective study with forty patients found that, following endoscopic ablation of dysplastic BE/EAC, p53 overexpression (determined by immunohistochemistry and confirmed by DNA sequencing) and persistent biologically active hr-HPV infection (types 16 and 18) were independently associated with persistent dysplasia/neoplasia.[117] The results of PCR-based DNA quality testing (b-globin) and an assessment of the presence of HPV DNA in 241 histologically verified archived EAC and GEJAC (gastro-esophageal junction adenocarcinomas) tissue specimens from an Australian population-based study were recently reported by Antonsson et al.[118] Each sample was examined three times for HPV DNA, and 233/241 specimens (201 EAC, 32 GEJAC) had a 97% DNA yield and acceptable quality. Out of 233 tumor specimens, none had a positive test result. The researchers firmly declared that "HPV is unlikely to cause EAC or GEJAC" and there was no indication of HPV DNA in the

tumor cells from esophageal adenocarcinomas. Future research could look into p53 and chronic hr-HPV infection as possible dysplasia/EAC risk markers in both BE screening and surveillance studies and therapeutic trials.

Prognostic value of HPV status in esophageal cancer

Numerous writers have assessed the predictive value of HPV-ESCC infection. The prognosis for patients with HPV-positive head and neck squamous cell carcinoma is consistently better than that of patients with HPV-negative tumors, as demonstrated by multiple retrospective clinical studies on oropharyngeal lesions. [119-120] However, the available data on HPV in ESCC is still sparse and inconsistent. According to Farahats et al,[121] esophageal cancers with high levels of p53 protein expression (likely caused by p53 mutations) were inversely correlated with HPV16 or 18 infections. The prognoses of two groups—one with p53 overexpression and the other with HPV16 or 18 infection-were significantly worse than those of the group without either condition. According to Hippeläinen et al,[122] HPV was not predictive for 11% of the 61 individuals with ESCC.

Several writers have been unable to demonstrate a meaningful correlation between HPV infection and patient survival. On the other hand, ESCC patients with HPV-positive tumors had better overall and disease-free survival, according to a recent set of research. When HPV status was taken into consideration as an independent prognostic factor for overall survival (OS) and progression-free survival among patients with ESCC, Cao et al.[123] reported that HPV-infected patients had better 5-year rates of overall survival (65. 9% vs. 43. 4% among patients with HPV-negative tumors; P = 0. 002 by the log-rank test). A conclusive conclusion is impossible due to the diversity of clinical data, which does not support a predictive role for HPV infection in ESCC. It now seems unlikely that HPV is clinically or etiologically important for ESCC, based on the evidence discussed above. Therefore, there is insufficient data to

support the idea that ESCC patients should undergo testing for HPV infection outside of research studies, and there is also insufficient data to support the idea that clinical practice or treatment plans for ESCC lesions should be altered in response to HPV status. However, Oei et al. [124] used ex vivo patient biopsies, in vivo tumor models, and cervical cancer cell lines infected with HPV 16 and 18 to investigate how HPV-positive cells react to heat. They discovered that by degrading E6, hyperthermia at 42 °C for 60 minutes activated the p53-dependent apoptotic pathway. This result emphasizes the distinction between HPV-positive and HPV-negative cells: HPV-negative cells required heat to promote these effects, while HPV-positive cells required radiation to increase p53 and trigger death. Therefore, more clinical research on the relationship between hyperthermia and other HPV-associated malignancies may result from these results.

EBV and OSCC

Five (31.3%) of the 16 instances of oesophageal cancer in our investigation tested positive for EBV. Jenkins et al. presented the first report of EBV DNA identification in OSCC in 1996.[125] They discovered that 1/16 of OSCC cell lines and 5/60 oesophageal tumor samples were positive using micro dissected tumor samples. Mizobuchi et al. used PCR to examine 41 surgical tissues and 12 OSCC cell lines for the presence of the EBV EBNA-1 gene, but they detected none.[126]

In 36 surgically removed OSCC, Yanai et al.'s second Japanese study found no EBER (EBV encoded RNA) -1-positive cell using ISH.[127] Similarly, an investigation conducted by ISH on 104 surgically removed OSCC in Thailand did not reveal any EBER-positive cancer cells.[128] Wang et al. used ISH and PCR amplification for the EBV BamHIW fragment to analyze 51 paraffin-embedded OSCC samples (9 well differentiated, 31 moderately differentiated, and 11 poorly differentiated tumors) from a high-risk region in Northern China for EBER.[129] The results were all negative. On the other hand, in a Taiwanese investigation,

EBV DNA was found by PCR in 11/31 (35.5%) of the OSCC patients.[130] EBER detection by ISH verified these findings. Awerkiew et al. examined the existence of EBER transcripts (ISH) and EBV DNA (PCR) in 72 OSCC, 40 OAC, and 43 OSCC from Russia. They discovered that while EBER transcripts were absent from tumor nuclei, EBV DNA was present in 34% of OSCC and 26% of OAC. However, out of the 24 cases with positive EBV DNA, 7 OSCC and 1 OAC had EBER transcripts found in the nuclei of lymphocytes infiltrating the tumor. As EBV did not persist in tumor cells, the authors correctly inferred a negative correlation.[131] Another negative investigation, published by Hong et al., found no EBV DNA in 30 OSCC and 2 OAC cell lines.[132] Wu et al.'s analysis of 164 oesophageal cancers (151 OSCC and 13 undifferentiated tumors) for EBV produced the most convincing positive finding. Ten (6.1%) tumor specimens were shown to have both EBV EBER and LMP-1 proteins by both ISH and IHC. These proteins were only found in undifferentiated carcinomas with significant lymphoid infiltration or poorly differentiated squamous cell carcinomas.[133]

Figure 10: Total esophagectomy with gastric pull-up For an EBV positive patient

EBV and OAC

A study involving 162 OAC, 92 cardia adenocarcinomas, and 89 gastric adenocarcinomas revealed that EBER transcripts were present in 0 (0%), 3 (3.3%), and 8 (8.1%) of the stomach adenocarcinoma samples.[134] EBER identification with ISH was 0 in OAC, 2 in GOJ (2.7%), and 12 in gastric cancer (4.4%) in another investigation involving 465 resected specimens of oesophageal and gastric adenocarcinomas (118 OAC, 73 GOJ adenocarcinomas, and 274 gastric adenocarcinomas).[135]

In our study, 56. 3% of tumors were in the lower third of the esophagus, while 43. 8% are found in the middle third. This indicates a higher prevalence of tumors in the lower third of the esophagus Shi et al. [136] retrospectively reviewed 2015 patients undergoing esophagectomy. In this series, the distribution of cancer location was upper (2%), middle (78%) and lower (20%).

Fig 11: Endoscopic Picture of Adenocarcinoma of esophagus

The most frequent site in the Choksi D et al. [65] study was the mid-esophagus, with 229 individuals, closely followed by the lower esophagus, with 208 patients. This is comparable to the Mumbai data listed in the National Cancer Registry of India. The lower esophagus was more involved in our analysis (37. 68%) than it was in the regional cancer registry (30%). This result contrasts with another study from India that found the mid-esophagus to be the most common place.[79] Nevertheless, in contrast to studies conducted in the West, our analysis did not reveal a trend toward a higher incidence of adenocarcinoma in the lower esophagus or lower esophageal malignancy. Actually, although not statistically significant, our analysis showed a modest decrease in the total number of lower esophageal malignancies. This may be due to the absence of risk factors that are common in the West, such as obesity, acid reflux illness, and other socioeconomic issues. However, our analysis revealed a statistically significant rise in the frequency of GEJ tumors of the adenocarcinoma type. Nevertheless, European country cancer registries have documented a rise in GEJ adenocarcinoma. A scientific assessment of the causes of this in our population is warranted. This may indicate a slow progression of the illness, similar to what was observed a few decades ago in the West. Similar findings from a recent international investigation were noted.[137]

The most often administered treatment in the current study is NACT + RT + TTE (18. 8%), which is followed by NACT + surgery (12. 5%) and defaulting treatment. Additional therapies consist of feeding jejunostomy, neoadjuvant therapies, palliative chemotherapy, and distal esophagectomy.

The two primary components of treatment for esophageal cancer are surgery and neoadjuvant concurrent chemoradiotherapy (CCRT).[138] For patients with locally advanced esophageal cancer, randomized trials have shown a strong benefit in survival rate when neoadjuvant chemotherapy and radiotherapy are used in conjunction with surgery.[139] According to Bognar et al., HPV infection is a poor prognostic factor in patients with ESCC

since it has been linked to a poor response to oncological treatment and a lower overall survival.[140] Thus, it is now unable to definitively establish a link between HPV infection and esophageal cancer. The aforementioned research's findings suggest that there may be a link between the prevalence of HPV and the incidence of EAs, however trustworthy information regarding HPV's effect on ESCC appears to be lacking. More research must be done on this matter.

GASTRIC CARCINOMA

Of the patients who had stomach cancer in the 30-40 age range, females constituted 20.0% of the total, while males comprised 18.2%. In the 40-50 bracket, females represent 40. 0% compared to males at 9. 1%. Conversely, in the >60 category, males made up 45. 5% of the total, surpassing females at 40. 0 %

Geographical differences in the frequency of GC can vary by a factor of 10, indicating that environmental or genetic factors may impact carcinogenesis and clinical pathological characteristics. Gastric cancer is extremely uncommon in all demographics and nations in adults under 50. The frequency of GC rises gradually with age until it reaches a plateau in the 55–80 age range. Because the incidence of GC in males is two to three times higher than in women, men are often more susceptible than women. [141-142] This implies that there are sex-specific differences in the incidence of GC, but it's crucial to highlight how geographic diversity affects it. [143-144] As a result, the incidence demonstrates a great deal of geographic diversity: over 50% of new cases are found in developing nations. The likelihood of GC development is higher in areas like East Asia (China and Japan), Eastern Europe, and Central and South America.[145] Australia and New Zealand, South Asia, North and East Africa, and North America are low-risk zones. The range of the ratio in Europe is 10–30%.[146] Alternative prevention strategies for gastric cancer (GC), which take into account a healthy diet, early diagnosis, and follow-up with appropriate treatment, can reduce the number of reported

episodes of the complex illness, particularly in the younger population.[147-148] among fact, GC is quite uncommon among young people and has a low prevalence in the under-45 age group, with no more than 10% of patients developing the condition.[149-151]

In the present study, adenocarcinoma accounted for 14 cases, representing 6. 3% of the total, while poorly differentiated cases total 2, comprising 75. 0%. This breakdown highlights the prevalence of adenocarcinoma with a notable proportion showing poor differentiation.

Moderately and poorly differentiated cases are equally prevalent, each comprising 37. 5% of the total cases, while adenocarcinoma with moderate differentiation represented the largest proportion. Adenocarcinoma, Adenocarcinoma stomach, and Gastric adenocarcinoma each contributed to smaller percentages, totaling 12. 5% collectively

Moderately differentiated adenocarcinoma constituted the highest proportion at 40. 0%, followed by poorly differentiated adenocarcinoma at 33. 3%. Adenocarcinoma stomach and gastric adenocarcinoma each represented 6. 7% of cases. Poorly differentiated cases had notably higher percentage within the poorly differentiated category at 50. 0%

Fig 12: Polypoidal growth around pylorus of stomach

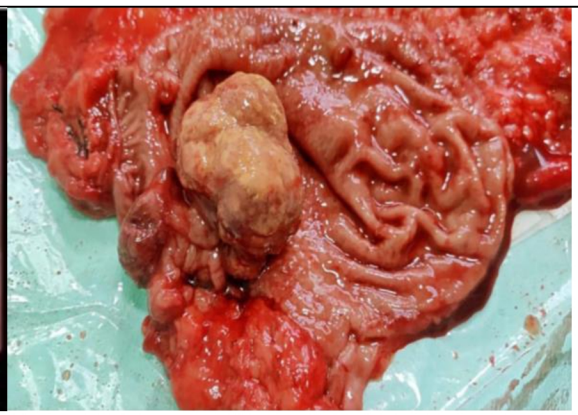


Fig 13: Polypoidal growth near pylorus of Stomach

HPV and Gastric Cancer

In our investigation, 2 (2.5%) of the stomach patients had HPV positive. Studies about the

function of HPV in GC have shown conflicting results. Publications about associations, both positive and bad, abound. However, a recent meta-analysis of fourteen studies examining the prevalence of HPV in 1205 controls and 901 gastric cancer patients found that the former had a pooled prevalence rate of 23.6%. The risk of gastric cancer was significantly correlated with HPV infection (OR = 1. 53, 95% CI 1. 00–2. 33, p = 0. 002).[126]

The part viruses play in the development of cancer has long been a topic of intense discussion. It is insufficient to prove causation when viral DNA, RNA, or proteins are only detected. However, it is well recognized that viruses like EBV are the cause of up to 10% of stomach malignancies. Given the strength of positive association studies, the significance of HPV in a sizable percentage of OAC is becoming more well acknowledged, however it is more debatable for OSCC.[126]

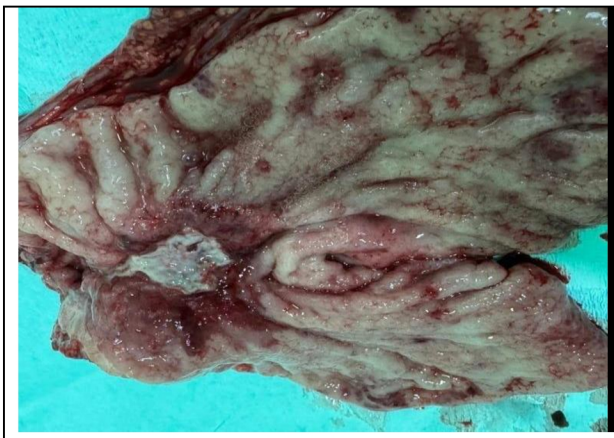


Fig 14: Ulcerative growth over body of stomach seen after gastrectomy

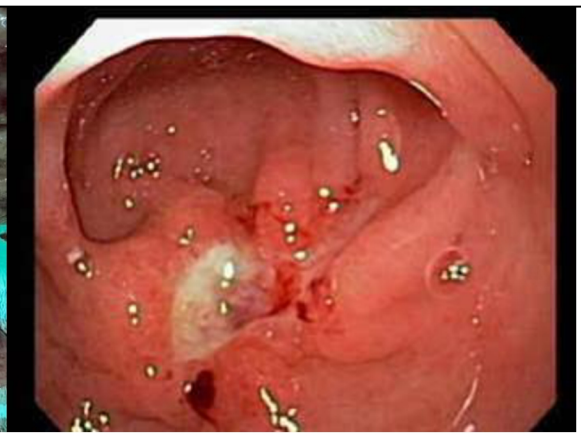


Fig 15: Ulcerative growth present in Body of stomach

Jafari-Sales et al. conducted a thorough investigation of the HPV and EBV prevalence in GC. HPV and EBV virus prevalence in GC were 10. 58% and 8. 58%, on average, respectively. In Turkey and Iraq, the greatest HPV and EBV prevalences were 37. 74% and 44. 44%, respectively. Asia (17.54%) and Africa (19.02%) had the highest chances of HPV and EBV in GC, respectively. The HPV virus was found using PCR and IHC. Eight of the fifty cancer samples tested positive for HPV by PCR and IHC, according to the findings. The mean

age of the HPV-positive samples was 62.87 ± 9.67. In comparison to women, men had more HPV-positive samples than women (5 samples vs. 3 samples). Nevertheless, no viral genomes were found in the control or non-malignant samples. HPV infection and GC were significantly correlated (P=0. 03).[128]

Using Real Time PCR, Yahyaapour et al. investigated the presence of three oncogenic viruses in neoplastic and non-neoplastic esophageal lesions: the human papilloma virus (HPV), the Epstein-Barr virus (EBV), and the Merkel cell polyomavirus (MCPyV). According to the findings, HPV DNA was discovered in 28 of the 68 samples from the non-neoplastic group (41.2%) and 27 of the 100 neoplastic esophageal lesions (27.0%). Three of the 68 samples in the non-neoplastic group (4.4%) and 10 of the 100 neoplastic cases (10%) had esophageal specimens with EBV DNA found in them.[129] Deniz et al. organized the available data regarding the links between HPV infections and oropharyngeal cancers and came to the conclusion that an HPV infection may contribute to the oncogenesis of gastrointestinal tract malignancies.[131] According to Milani et al., individuals with gastric cancer (GC) had considerably greater frequencies of HPV and EBV than those in the control group, while those with esophageal cancer (EC) had higher frequencies of JCV infection than those in the healthy group. When compared to the healthy patients, JCV infection dramatically raised the risks of CRC and EC incidence by 11. 8 and 10. 2 times, respectively. Furthermore, a 10.8- and a 6.7-fold increased risk of gastric cancer and colorectal cancer, respectively, was linked to HPV and EBV.[132]

EBV and Gastric Carcinoma

Six patients (37.5%) of gastric cancer in the current investigation were positive for EBV. To shed light on the correlation between EBV infection and gastric cancer, Tavakoli et al. conducted a meta-analytic analysis of the prevalence of EBV in patients with gastric cancer. Using internet databases, a literature search for English-language articles was done

electronically until July 1st, 2019. Using a random-effects model, the pooled EBV prevalence and 95% confidence intervals (CIs) were calculated. For case-control studies, the pooled odds ratio (OR) and its 95% confidence interval (CI) were calculated to ascertain the relationship between EBV and stomach cancer. To determine the pooled estimates of ORs, data from case-control studies using matched and non-match pairs designs were subjected to two distinct analyses. The combined prevalence of EBV in 20,361 individuals with gastric cancer was 8. 77% (95% CI: 7. 73–9. 92%; I2 = 83. 2%), according to the data. Twenty investigations, involving pairs of normal tissue next to the tumor and from 4116 individuals with stomach cancer, were conducted using matched pairs design. For studies using matched pairs design, the pooled ORs were 18. 56 (95% CI: 15. 68–21. 97; I2 = 55. 4%), whereas for studies using a non-matched pairs design, the pooled ORs were 3. 31 (95% CI: 0. 95–11. 54; I2 = 55. 0%). Male cases had a considerably larger proportion of EBV-associated gastric cancer (10. 83% vs. 5. 72%) than female cases did (P < 0.0001). Nevertheless, compared to males (14. 07; 95% CI: 10. 46–18. 93; I2 = 49. 0%), the pooled OR estimate for EBV-associated gastric cancer was considerably higher in females (21. 47; 95% CI: 15. 55–29. 63; I2 = 0%) (P = 0. 06). EBV was more common in the body (11.68%) and cardia (12.47%) than in the antrum (6.29%) (P = 0.0002). The scientists concluded that an EBV infection increases the risk of stomach cancer by more than 18 times based on their findings. Men are less likely than women to acquire EBV-associated gastric cancer, even though male patients with the disease had a higher incidence of EBV than female patients. The results of the study demonstrated that utilizing normal tissues next to tumors as the control group yields more reliable and accurate conclusions on the connection between EBV infection and stomach cancer.[133] Meta-analyses have partially validated the greater frequency of EBVaGC in males observed in most investigations. [155-152] In terms of risk estimates, this preponderance declines with age; however, EBVaGC is more common in younger individuals than EBVnGC. [155–152]

1990 saw the discovery of the first correlation between gastric epithelial lymphatic carcinoma (GC) and EBV, or epithelial lymphatic carcinoma.[156] Further research has also revealed a link between EBV and stomach adenocarcinoma, which may suggest that EBV plays a significant part in the pathophysiology of the disease. Accordingly, these results imply that 10% of GCs globally are linked to EBV.[159–157] Early in the G phase, EBV infection is effective because it may constantly infect a cell through monoclonal growth. Despite a multitude of investigations into the mechanisms behind the genesis and progression of GC and positive EBV, no correlation was observed between EBV titer and GC risk.[160] According to studies, latent EBV infection and latent EBV gene expression as a co-factor enhance carcinogenicity, which results in disruption of cell pathways, aberrant DNA methylation, and aberrant host genome structure and function of immune cells.[161]

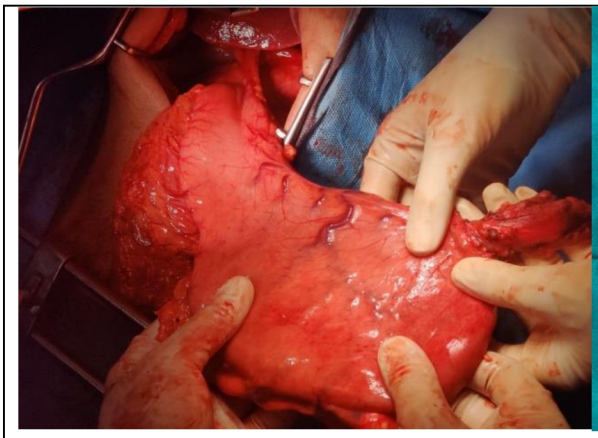


Figure 16: Gastrectomy for Carcinoma Stomach and body

Figure 17: Thickening of Antrum of stomach

EBV is the second most important viral component linked to the onset of gastric cancer, behind H. pylori infection. Approximately 10% of gastric carcinomas are EBV-associated gastric carcinomas (EBVaGC). The main reason for the recruitment of EBV-infected B-lymphocytes around gastric epithelia is stomach inflammation, which will eventually raise the

frequency of EBV infection of the epithelia; however, there is conflicting evidence regarding the relationship between HPV and gastric cancer. Like EBV infection, HPV triggers the NFκB signaling pathway, which is essential for cancer cell survival and proliferation. It was also shown that the interferon regulatory factor 8 (IRF8), in conjunction with PU, promotes the production of EBV lytic genes. 1. Regardless of the disease's clinical stage, Snietura et al. studied 84 Central European patients who underwent surgery for stomach adenocarcinoma. Every person tested negative for the highly carcinogenic HPV subtypes. Given the population of Central Europe and the previously described studies, a correlation between GC and HPV infection is unlikely.[162] However, research from China suggested that GC risk was elevated by HPV infections.[163] A meta-analysis of 1917 cases revealed that HPV may have a strong correlation with the pathophysiology of gastric cancer. Among all the GC patients, the combined HPV prevalence was 28. 0% (95% CI: 23. 2%, 32. 7%). On the other hand, compared to patients from non-Chinese locations, the HPV prevalence was considerably greater in Chinese patients (31% vs. 9%, $I2 = 95.0\%$, $p < 0.01$). Finding HPV in the cells of GC precursor lesions, such as gastric dysplasia or adenoma, is the only way to verify any connections.[164] Because of the strong likelihood of heterogeneity bias, the association between HPV infection and GC appears dubious based on the data that are currently available. Further research using a more sophisticated methodology is required to validate the above-described association.

8. 4% of stomach cancers (mostly adenocarcinomas) were linked to the Epstein-Barr virus in the research by Rajendra et al. [165] Compared to antral tumors (5. 2%), proximal malignancies, such as corpus and cardia, had a significantly higher likelihood of being EBV positive (13. 1% and 13. 6%, respectively). According to the TCGA genomic analysis, EBV positivity accounts for about 9% of stomach malignancies. Burke et al. used PCR in 1990 to report the first case of EBV-positive gastric neoplasia and lymphoepithelial carcinoma.[166] However, approximately 1% to 4% of stomach malignancies are lymphoepithelial-like (LEL)

tumors, of which 90% are EBV-positive. In comparison to virus-negative lesions, the authors noted that patients with EBV-positive gastric tumors are typically younger, more frequently male, have a higher correlation with smoking, are more likely to occur in a distal location, have fewer lymph node metastases, and have a better prognosis.

The most well-known virus linked to gastric adenocarcinoma is the Epstein-Barr virus (EBV), which is thought to be responsible for 10% of cases.[167] Male patients are more likely to develop EBV-associated gastric cancer, which is characterized by a high frequency of the disease in the upper portion of the stomach and multiplicity. EBV-induced gastric carcinogenesis has been linked to several variables, including changes in cell cycle pathways, inflammatory changes in the gastric mucosa, and hypermethylation of tumor suppressor genes. Aversa et al. did, however, report a low EBV prevalence in stomach cancer in a Chinese population with a high incidence.[168] Aversa et al. observed a rate of just 0.9% in cardia localization, despite prior findings showing a very high positive rate in this area. Numerous studies have demonstrated that patients with stomach cancer linked to EBV may respond favorably to immunotherapy and have a favorable prognosis. [169-170] Tumor-infiltrating lymphocytes may increase cell-mediated cytotoxicity and may be more susceptible to chemotherapeutic drugs, albeit the exact causes of this are still unknown. More investigation into the carcinogenic pathway is necessary, as there are still many unanswered questions about the carcinogenesis of stomach cancer induced by EBV.

The body accounted for 31.3% of all sites in our analysis, with the fundus coming in second at 18.8%. The pylorus, greater curvature, and lesser curvature are further regions. Particularly in the stomach residual following a partial gastrectomy, EBVaGC preferentially settles in the middle and upper regions of the stomach. Two times as many cases of EBVaGC were found in the upper or middle stomach as in the lower stomach, according to a Japanese study that examined the clinicopathological characteristics of the disease in 1,132 patients

following various gastrectomy techniques.[167] The proximal portion of the stomach showed a prevalence of EBVaGC in the large Dutch D1D2 experiment, which comprised 566 patients with both EBVnGC and EBVaGC.[168] Even when the comparison is limited to non-remnant malignancies in the middle stomach and cardia, rates of EBV positive are higher in remnant GC.[171]

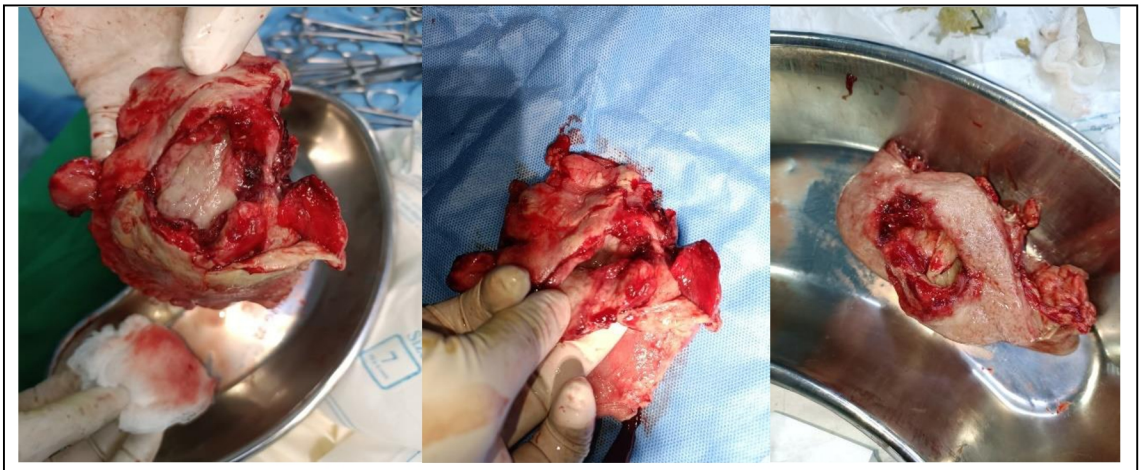


Figure 18. Malignant perforation secondary to gastric carcinoma (Intraoperative specimen)

Additional research has also revealed that EBVaGCs preferentially grow in the proximal part of the stomach, encompassing the cardia, fundus, and body.[172] The predominant histological subtypes of this region are lymphoepithelioma-like carcinoma and Crohn's disease-like lymphocytic response. Tumor-infiltrating lymphocytes (TILs) outnumber tumor cells in approximately 90% of lymphoepithelioma-like carcinomas, which are EBV-positive. On the other hand, TIL infiltration is less common in the antrum region of the stomach, where EBVnGCs are predominant. A positive EBV status is often linked to Gastritis cystica profunda, a precancerous lesion characterized by enhanced proliferative activity and cystic gastric glands within the submucosa. EBVaGCs' immunophenotyping shows an equitable distribution between a null phenotype, which expresses neither intestinal-like nor gastric-like phenotypes and a gastric-like phenotype, which expresses both the MUC5AC and MUC6 mucins.

The aetiology of about 20% of cancer cases is viral, and in this context, the Epstein-

Barr virus (EBV) is linked to multiple cancer forms, including stomach cancer. Adenocarcinomas comprise approximately 95% of all instances of stomach cancer, and 10% of these cases are linked to EBV.[173] As a result, 10% of GCs have been identified as EBV-positive; however, there is not enough data to conclude that EBV plays a unique etiological role in the formation of GCs. The factors of the patient, such as gender, age, anatomical subsite, and geographic location, influence the type of stomach cancer that is positive for EBV. The Cancer Genome Atlas (TCGA) network classifies EBV-positive malignancies as making up approximately 9% of all cancers; however, it is important to note that the prevalence varies by geographic region, with Asia having a higher frequency than Europe (about 5%). More men are afflicted by EBV-associated stomach cancer, which leads the world in virus-related mortality overall. In GC, the number of EBV-related mortality increases exponentially with age, particularly after the age of sixty. EBV can enter the stomach through saliva as a free viral particle in infected oropharyngeal epithelial cells and B lymphocytes. The cardia, or upper part of the stomach, and the non-cardia, or bottom section of the stomach, are the two topographical sub-sites into which the stomach is typically divided. When EBV enters the stomach, it becomes less contagious, which helps to explain why EBV-associated gastric malignancies are more common in the upper portion of the organ (the cardia-GC subtype).

Palliative chemotherapy is the most common treatment in this study (25.0%), and is followed by several surgical procedures, including subtotal gastrectomy, proximal and distal gastrectomy, and neoadjuvant chemotherapy. For the treatment of esophageal cancer, a multidisciplinary approach incorporating surgery, chemotherapy, and radiation therapy has been devised. The randomized control trial for ESCC patients was carried out by Ando et al., who demonstrated that an esophagectomy followed by preoperative chemotherapy could increase survival.[174] Moreover, the effectiveness of preoperative chemoradiotherapy was assessed by the Dutch CROSS study.[175] Thus, individuals with esophageal cancer who

underwent surgery and then chemoradiotherapy had a longer overall survival than patients who had surgery alone. Chemoradiotherapy or perioperative chemotherapy are currently recognized as standard treatments globally.

75% showed no evidence of cancer, while 13% had no margin involvement. Distal and proximal margin involvement each accounted for 6% of cases, with one case exhibiting a positive distal margin of 2cm.

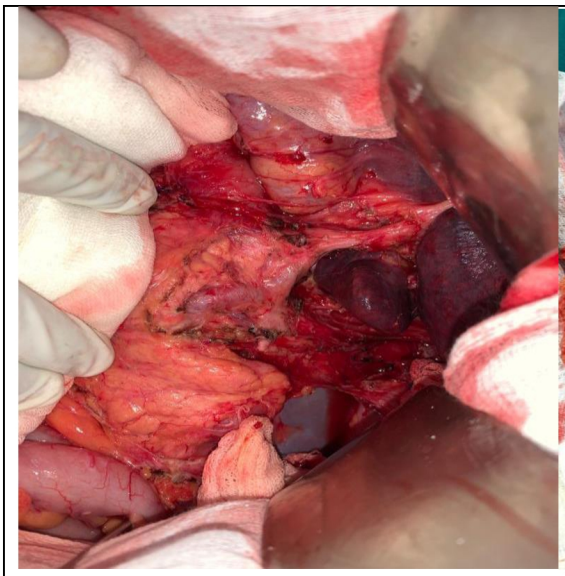


Figure 19: Post gastrectomy Margins

Figure 20: Post Gastrectomy Specimen with Omentum

INVOLVEMENT OF LYMPH NODES

In the present study, for the esophagus, 40% (4 out of 10) of cases had Lymph nodes involvement in the 0-5 range, and 60% (6 out of 10) fall in the >5 range. For the stomach, 100% (8 out of 8) of cases fall in the 0-5 range, with no cases in the >5 range. The Fisher Exact test yields a P-value of 0. 01, indicating a statistically significant difference between the distributions in the esophagus and stomach. This suggests that the variable's distribution differs significantly between the two organs.

Even in the early stages of the disease, esophageal cancer has a high incidence rate of lung metastasis compared to other gastrointestinal malignancies. Moreover, the primary route

of lymph node metastasis is from the cervix to the abdominal field. Takeuchi et al. described mapping of patients with superficial esophageal squamous cell carcinoma (ESCC) to the sentinel lymph nodes (SLNs), which are the first lymphatic nodes to receive drainage from a primary tumor site.[176] Regardless of where the tumor was located, there were, on average, 4. 7 SLNs in the report, with varying locations from the cervical to the abdominal field. Additionally, Akutsu et al. examined the distribution of metastatic LN in cT1 esophageal cancer and reviewed ESCC patients who were enrolled in a prospective multi-institutional randomized trial.[177] As a result, tumors in the upper thoracic esophagus (Ut) were frequently related with upper mediastinal LN metastases, while tumors in the lower thoracic esophagus (Lt) were frequently associated with abdominal nodes. However, LN metastases from the cervical field to the abdominal field was noted in the middle thoracic esophagus (Mt). Tachimori et al. looked at the distribution of lung nodule metastases in 356 patients with esophageal squamous cell carcinoma (ESCC) undergoing transthoracic esophagectomy with 3-FU.[178] According to the findings, upper mediastinal LN metastasis was commonly seen in individuals with Mt or Lt illness. Based on those studies, prolonged LN dissection was identified as a potentially useful treatment for managing trans-lymphatic metastases in esophageal cancer.

Yamashita et al. used nationwide data from Japan to examine the spread of LN metastases in esophagogastric junction cancer.[179] and discovered that the location of LN metastasis was substantially influenced by the tumor epicenter. When comparing the histology and LN metastatic location, squamous cell carcinoma metastasis was more common in the upper and middle mediastinum than adenocarcinoma. Tumor histology should therefore be taken into consideration to ascertain the range of LN dissection, especially in cases of malignancy of the esophagogastric junction.

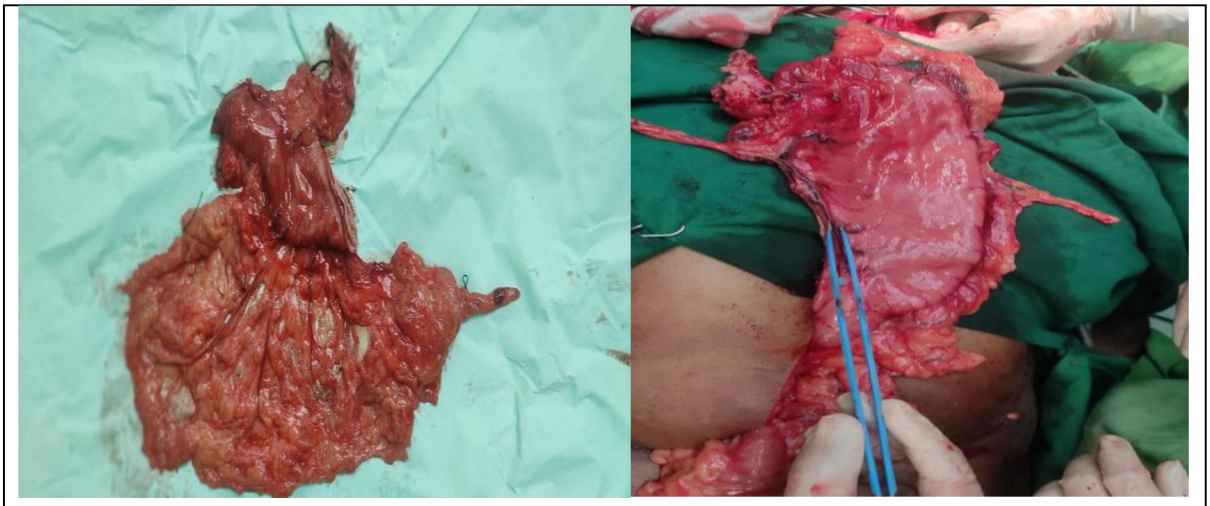


Figure 21: Subtotal Gastrectomy with Lymph node Dissection

It is challenging to harvest regional lymph nodes from stomach cancer since there are a lot of them, many of them are small, and metastases can happen even in these little lymph nodes. But up until now, node harvesting's accuracy has received little attention. Pathologists are likely to handle collected nodes globally. Pathologists can use the "palpitation method," which is arguably the most widely used technique for differentiating lymph nodes in the world, but surgeons or specialists at specialized facilities can check a larger number of lymph nodes. In therapeutic settings, it is common to target more than 15 lymph nodes for collection. The real number of lymph nodes affected is larger, though, and prior research has indicated that after a D2 distal gastrectomy, more than 40 lymph nodes may be removed. Numerous investigations have indicated that a higher number of lymph nodes extracted is linked to a better prognosis. [180-182] Put another way, even though lymph node harvesting is a significant predictive component, quality control is still lacking.

In T1 EGC, the overall incidence of LN metastases is 10–20%. Tumor features, including size, cancer depth, histologic type, and lympho-vascular invasion presence, are critical factors in determining the probability of metastasis. For instance, the incidence of LN

metastasis was found to be 14. 1% overall in the Roviello et al. Study, which evaluated 652 instances of resected EGC; 4. 8% versus 23. 6% for mucosal versus submucosal cancer. The likelihood of smaller cancers being linked to positive nodes was much lower: 9% compared to 20% and 30% for tumors with diameters of less than 2 cm, 2 to 4 cm, and more than 4 cm, respectively. A low incidence of lung metastases (1.7%) was linked to well-differentiated type I and IIa T1 tumors with a diameter of less than 2 cm and nonulcerative type IIc T1 tumors with a diameter of less than 1 cm in the Sano et al. Study.[183]

There are not enough research examining the development of LN metastasis from advanced gastric cancer (AGC) to EGC and the state of AGC. More than 60% of untreated EGCs are expected to proceed to AGC within five years, according to a Japanese report.[184] According to Nakajima et al., the incidence of gastric cancer's LN metastases with invasion to MP, SS, SE, and SI was 52.2%, 66.9%, 74.4%, and 82.6%, in that order.[185] Assessing the degree and existence of LN metastasis in AGC prior to surgery is challenging, though. The assessment of the incidence of LN metastases in AGC involves two concerns: First, the incidence and distribution of LN metastasis are influenced by a variety of parameters, including the location, depth, size, macroscopic type, and histology type of the AGC. Second, examination techniques like H and E staining, immunohistochemical staining, and reverse polymerase chain reaction have an impact on the identification of LN metastases with resected materials.

CONCLUSION

CONCLUSION

In the present study, we observed the presence of EBV virus infection in both esophageal and gastric cancers, while HPV was not prevalent in Oesophageal, only a minority of the patients with gastric cancers were positive for EBV.

This study also showed an association between the number of nodes retrieved for virus-positive cases compared to those that were negative for the virus; hence, going forward, the number of nodes retrieved can be increased for better clearance of the viral burden reducing the chances of spread secondary to the viral load.

Further studies involving larger group of patients is warranted to establish the prevalence of the role of the viruses, the further planning of treatment modalities (surgery/ radiotherapy and chemotherapy/ targeted therapy) and for the prognostication of Esophageal and Gastric tumors.

However, as the study is confined to our institution, the Prevalence of EBV in Esophageal and gastric carcinoma is significant with respect to the study population.

SUMMARY

SUMMARY

- In the present study, there were a total of 32 cancer cases. Out of these, 16 (50%) were esophageal carcinoma and 16 (50%) were stomach carcinoma.
- HPV positivity was not observed in any case of esophagus carcinoma, while it was positive in 2(2. 5%) gastric cases.
- EBV was positive in 5 (31. 2%) esophagus and 6 (37. 5%) gastric carcinoma cases.
- Oesophageal carcinoma more prevalent in males (56. 3%) compared to females (43. 8%). Occurrence of esophageal carcinoma in older females and younger males.
- Among the 16 patients with esophagus carcinoma, squamous cell carcinoma was the most common type (68. 8%), followed by adenocarcinoma (25. 0%).
- There were no positive cases of HPV detected in cases of cancer esophagus.
- Out of the total 16 cases of oesophageal cancer, 5 (31. 3%) were positive for EBV
- 56. 3% of tumors were in the lower third of the esophagus, while 43. 8% are found in the middle third
- The most common treatment for oesophageal cancer was NACT + RT + TTE (18. 8%), followed by defaulted treatment and NACT + surgery (both 12. 5%).
- HPV positivity was found in 2(2. 5%) in gastric cases
- EBV was positive in 6 (37. 5%) gastric carcinoma cases.
- The body was the most common site of gastric carcinoma, 31. 3%, followed by the fundus at 18. 8%.
- Palliative chemotherapy constitutes the most prevalent treatment for gastric carcinoma 25. 0%, followed by various surgical interventions such as proximal and distal gastrectomy, subtotal gastrectomy, and neoadjuvant chemotherapy.

LIMITATIONS AND RECOMMENDATIONS

LIMITATIONS AND RECOMMENDATIONS

Major limitation of the study was small sample size. The results of this study are more likely to contain type II statistical errors, so our findings need to be verified by carrying out a larger, multi-centric randomized trial. As with any technology, there are limitations to the modality that need to be considered, even if the research seems to support the correlation between EBV and HPV with esophageal and gastric carcinoma. However, EBV and HPV testing can be incorporated into the recent guideline in gastrointestinal carcinoma testing so are to consider immunotherapy.

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ANNEXURES

ANNEXURES

ANNEXURE I

PATIENT PROFORMA

SUBJECT EVALUATION

Date:

Time:

Name:
Age:
Sex:
Occupation:
UHID number:
Presenting complaints:
Past history:
Family history:
History of habits:

Phone number:
Address:
DOA:
DOS:
DOD:

GENERAL PHYSICAL EXAMINATION:

- Built and nourishment:
- Pallor/Cyanosis/Icterus/Clubbing/edema/Generalized lymphadenopathy

VITAL DATA:

- Pulse:
- Temperature:
- BP:
- Respiration rate:

SYSTEMIC EXAMINATION

- Respiratory system:
- Cardio vascular system:
- Central nervous system:
- Per abdomen:

INSPECTION:
PALPATION:
PERCUSSION:
AUSCULTATION:

- **Investigations:**

CBC
CECT thorax:
CECT (ABDOMEN+PELVIS)
USG(ABD+PELVIS):
LFT:
EBV
HPV

ANNEXURE II- INFORMED CONSENT FORM

I Mr./Mrs. _____have been explained in my own understandable language, that I will be included in a study title, "**CORRELATION OF HUMAN PAPILLOMA VIRUS AND EPSTEIN BARR VIRUS IN ESOPHAGEAL AND GASTRIC CARCINOMA IN A TERTIARY CARE CENTER"**

I have been explained that my clinical findings, investigations, findings will be assessed and documented for study purpose.

I have been explained my participation in this study is entirely voluntary and I can withdraw from the study any time and this will not affect my relation with my doctor or treatment for my ailment.

I understand that the medical information produced by this study will become part of institutional records and will be kept confidential by my said institute.

I agree not to restrict the use of any data or result that arise from this study provided such a use is only for scientific purpose(s).

I have been explained that all the cost will be taken by the primary instigator.

I have principal investigator mobile number for enquiries.

I have been informed that standard of care will be maintained throughout the treatment period.

I in my sound mind give full consent to be added in the part of this study.

Signature of the patient:

Name:

Date:

Place:

Signature of the witness:

Name:

Relation to patient:

ANNEXURE III - PATIENT INFORMATION SHEET

STUDY TITLE: "**CORRELATION OF HUMAN PAPILLOMA VIRUS AND EPSTEIN BARR VIRUS IN ESOPHAGEAL AND GASTRIC CARCINOMA IN A TERTIARY CARE CENTER**"

STUDY SITE: R.L Jalappa Hospital and Research Centre, Tamaka, Kolar.

This is to inform you that,

The purpose of the study is explained in detail to us and all information collected is for study purpose only. The data collected is submitted to the department of surgery, SDUMC, Kolar and confidentiality ensured. The merits and demerits explained briefly to us.

All Patients diagnosed with carcinoma esophagus and carcinoma stomach will be included in this study. Patients in this study will undergo routine investigations, CBC, RFT, CECT thorax, CECT abdomen and pelvis, previous biopsy reports. Patients planned for either a endoscopic biopsy or intraoperative sampling along with the samples will be sent for testing and checking positivity for HPV & EBV in the biopsy samples.

Please read the following information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in the study, we will collect information (as per proforma) from you or a person responsible for you or both. Relevant history will be taken. This information collected will be used only for dissertation and publication.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. This study has been reviewed by the Institutional Ethics Committee and you are free to contact the member of the Institutional Ethics Committee.

There is no compulsion to agree to this study. The care you will get will not change if you do not wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

For further information contact:
Dr. NEHA ULLALKAR [post graduate]
Department of General Surgery
SDUMC, Kolar
Phone number
9769992755.

left thumb impression/signature of the patient

left thumb impression / signature of the witness

MASTER CHART

SR. NO.	NAME	AGE	SEX	ADDRESS	UHID	IP NUMBER	DTAE OF ADMISSION	DATE OD DISCHARGE	TYPE OF CARCINOMA	HISTOPATHOLOGY	DIFFRENTIATION	AREA OF TUMOR	STAGE	BIOPSY NUMBER		HPV	MODE OF TREATMENT	NO. OF NODES RETRIVED	NO OF NODES POSITIVE	MARGINS POSITIVE
1	REDAPPA	62	MALE	MULBAGAL	143586	24814	30/09/2022	06/10/2022	ESOPHAGUS	SQUAMOUS CELL CARCINOMA	MODERATELY DIFFRENTIATED	MIDDLE 1/3RD OF ESOPHAGUS	-	B/2384/22	POSITIVE	NEGATIVE	DEFAULTED			
2	AYYAPPA REDDY	66	MALE	SHRINIVASPURA	158632	28156	09/11/2022	02/12/2022	STOMACH	ADENOCARCINOMA	MODERATELY DIFFRENTIATED	FUNDUS	PT4AN2BMX-IIIA	B/2834/22	POSITIVE	POSITIVE	PROXIMAL GASTRECTOMY	12	6 (3 SHOW EXTRA CAPSULAR EXTENTION)	NO MARGIN INVOLVEMENT
3	VANITHA C	36	FEMALE	KOLAR	150012	26222	17/11/2022	24/11/2022	STOMACH	ADENOCARCINOMA	MODERATELY DIFFRENTIATED	FUNDUS	pT2N0MX-IIIB	B/2826/22	POSITIVE	NEGATIVE	PROXIMAL GASTRECTOMY	21	2(2 SHOW ENE))	NO EVIDANCE OF CANCER
4	PRAMEELAMMA	55	FEMALE	KOLAR	183246	42334	06/04/2023	09/05/2023	ESOPHAGUS	SQUAMOUS CELL CARCINOMA	WELL DIFFRENTIATED	MIDDLE 1/3RD OF ESOPHAGUS	pyT1BN2MX-III	B/1395/23	POSITIVE	NEGATIVE	TTE	6	5(3 SHOW ENE)	NO EVIDANCE OF CANCER
5	NAGRAJA CHARI	60	MALE	CHINTAMANI	78100	23745	19/09/2022	14/10/2022	STOMACH	ADENOCARCINOMA	POORLY DIFFRENTAITED	BODY OF STOMACH	ypT2N3AMX-IVB	B/2823/22	NEGATIVE	NEGATIVE	SUBTOTAL GASTRECTOMY	0	0	NIL
6	NARAYANAMMA	46	FEMALE	SHRINIVASPURA	95228	19881	04/08/2022	09/08/2022	STOMACH	ADENOCARCINOMA	MODERATELY DIFFRENTIATED	PYLORUS OF STOMACH	ypT2N3AMX-IIIB	B/2819/22	NEGATIVE	NEGATIVE	NACT+ SURGERY	10	0	NIL
7	DEVRAJA N	47	MALE	MALUR	17459	34481	07/02/2023	15/02/2023	STOMACH	ADENOCARCINOMA	POORLY DIFFRENTAITED	LESSER CURVATURE	pT3N1MX-IIB	B/2834/22	NEGATIVE	NEGATIVE	PARTIAL GASTRECTOMY	19	1	DISTAL AND PROXIMAL MARGIN INVOLVED
8	BYCHAPPA	62	MALE	KOLAR	146383	25359	02/10/2022	26/10/2022	STOMACH	ADENOCARCINOMA	MODERATELY DIFFRENTIATED	BODY OF STOMACH	-	B/2684/22	NEGATIVE	NEGATIVE	PALLATIVE CHEMOTHERAPY			
9	ASHA	36	FEMALE	BANGALORE	209387	44569	03/05/2023	13/06/2023	ESOPHAGUS	SQUAMOUS CELL CARCINOMA	WELL DIFFRENTIATED	MIDDLE 1/3RD OF ESOPHAGUS	-	B/4984/23	NEGATIVE	NEGATIVE	NACT+ SURGERY	22	10(5 SHOW EXTRA NODAL EXTENTION)	
10	Y B REVE GOWDA	59	MALE	KOLAR	11426	20559	12/08/2022	19/09/2022	ESOPHAGUS	SQUAMOUS CELL CARCINOMA	WELL DIFFRENTIATED	MIDDLE 1/3RD OF ESOPHAGUS	ypT3N1MO	N/1495/05	NEGATIVE	NEGATIVE	NACT+ SURGERY	10	1	PROXIMAL MARGIN SHOWS DYSPLASTIC CELLS
11	KRISHNAPPA	68	MALE	HOSKOTE	121975	23192	13/09/2022	22/09/2022	ESOPHAGUS	POORLY DIFFRENTIATED	POORLY DIFFRENTAITED	LOWER 1/3RD OF ESOPHAGUS	-	B/2174/22	NEGATIVE	NEGATIVE	DEFAULTED			
12	THIPAMMA	60	FEMALE	KOLAR	231040	44914	08/05/2023	29/05/2023	ESOPHAGUS	ADENOCARCINOMA	MODERATELY DIFFRENTIATED	LOWER 1/3RD OF ESOPHAGUS	-	B/4144/23	NEGATIVE	NEGATIVE	FEEDING JEJUNOSTOMY			
13	VENKATAMMA	55	FEMALE	KOLAR	229923	49952	07/07/2023	05/08/2023	ESOPHAGUS	SQUAMOUS CELL CARCINOMA	WELL DIFFRENTIATED	LOWER 1/3RD OF ESOPHAGUS	YpT1AN3MX-IVA	A/2955/99	NEGATIVE	NEGATIVE	NACT+RT+TTE	22	8(2 SHOW ENE)	NO MARGINS
14	BASAPPA	86	MALE	MULBAGAL	149593	26068	15/10/2022	16/11/2022	STOMACH	ADENOCARCINOMA	POORLY DIFFRENTAITED	PYLORUS OF STOMACH	-	B/2994/22	NEGATIVE	NEGATIVE	GJ+JJ+SUPPORTIVE TREATMENT			
15	VENKATAMMA	60	FEMALE	MULBAGAL	233094	55237	25/08/2023	29/08/2023	ESOPHAGUS	SQUAMOUS CELL CARCINOMA	WELL DIFFRENTIATED	LOWER 1/3RD OF ESOPHAGUS	-	B/5394/23	NEGATIVE	NEGATIVE	NACT	38	5(2 SHOW ENE)	MARGINS NEGATIVE
16	CHANDRAPPA	48	MALE	KOLAR	213576	43508	20/04/2023	23/05/2023	ESOPHAGUS	SQUAMOUS CELL CARCINOMA	MODERATELY DIFFRENTIATED	MIDDLE 1/3RD OF ESOPHAGUS	ypT4AN2MX-IVA	A/2334/35	POSITIVE	NEGATIVE	NACT+RT+TTE	3	3(ALL SHOW ENE)	CIRCUMFRENCIAL MARGIN INVOLVED
17	NAGAPPA	58	MALE	CHINTAMANI	190842	40870	20/03/2023	01/04/2023	ESOPHAGUS	ADENOCARCINOMA	MODERATELY DIFFRENTIATED	LOWER 1/3RD OF ESOPHAGUS	ypT1BN0MX	B/2840/22	POSITIVE	NEGATIVE	NACT+SURGERY	21	6(5 SHOW ENE)	DISTAL MARGIN POSITIVE FOR DYSPLASTIC CELLS IN
18	VENKATAMMA	72	FEMALE	MULBAGAL	123733	20869	25/08/2022	12/09/2022	STOMACH	ADENOCARCINOMA	POORLY DIFFRENTAITED	BODY OF STOMACH	ypT3N3M0-III	B/2820/22	NEGATIVE	NEGATIVE	NACT+SURGERY			
19	NARAYANSWAMI S	59	MALE	MULBAGAL	230685	44861	07/05/2023	30/05/2023	ESOPHAGUS	ADENOCARCINOMA	POORLY DIFFRENTAITED	LOWER 1/3RD OF ESOPHAGUS	T3N3MX-IVA	B/4084/23	POSITIVE	NEGATIVE	TTE	20	11 (7 WITH EXTRANODAL EXTENTION)	PROXIMAL AND DISTAL ENDS FREE
20	NARAYANAMMA	56	FEMALE	MULBAGAL	135636	26165	17/10/2022	22/10/2022	ESOPHAGUS	SQUAMOUS CELL CARCINOMA	MODERATELY DIFFRENTIATED	MIDDLE 1/3RD OF ESOPHAGUS	ypT2N3MX-IVA	N/1525/61	NEGATIVE	NEGATIVE	NACT+RT+TTE	10	2	NIL
21	NARAYNSWAMI	36	MALE	KOLAR	242819	47352	06/06/2023	12/07/2023	STOMACH	ADENOCARCINOMA	MODERATELY DIFFRENTIATED	DISTAL STOMACH AND PYLORUS	pT4aN3aMx	F/37/23	POSITIVE	NEGATIVE	DISTAL GASTRECTOMY WITH GJ+JJ	32	21(11 SHOW EXTRANODAL EXTENTENTION)	MARGINS ARE FREE
22	KRISHNAPPA	51	MALE	HOSKOTE	286781	67676	25/09/2023	30/09/2023	STOMACH	ADENOCARCINOMA	POORLY DIFFRENTAITED	BODY OF STOMACH	pT3aN2Mx	B/3789/23	POSITIVE	NEGATIVE	SUBTOTAL GASTRECTOMY WITH GJ AND JJ	20	4(NO ENE)	DISTAL MARGIN IS 2CM POSITIVE
23	VEKNATRAMAPPA	69	MALE	CHINTAMANI	204046	52007	31/07/2023	12/08/2023	STOMACH	ADENOCARCINOMA	ADENOCARCINOMA STOMACH	GREATER CURVATURE	-	B/731/2023	POSITIVE	POSITIVE	PALLATIVE CHEMOTHERAPY			
24	JAVEED PASHA	36	MALE	KOLAR	246685	48078	20/06/2023	15/07/2023	STOMACH	ADENOCARCINOMA	MODERATELY DIFFRENTIATED	LESSER CURVATURE AND DISTAL STOMACH	pT2N0Mx	F/36/23	NEGATIVE	NEGATIVE	DISTAL GASTRECTOMY WITH GJ+JJ	31	0	NOT INVOLVED
25	CHIKKA VENKATRAMAPPA	62	MALE	KOLAR	222271	43043	22/04/2023	01/06/2024	STOMACH	ANDENOCARCINOMA	GASTRIC ADENOCARCINOMA	ANTIPYLORIC REGION OF STOMCH	-	B-1397-23	POSITIVE	NEGATIVE	PALLATIVE CHEMOTHERAPY			
26	LAKSHMAMMA	58	FEMALE	CHIK BELAPUR	211250	40698	17/03/2023	03/04/2023	ESOPHAGUS	SQUAMOUS CELL CARCINOMA	MUSCENIOUS CARCINOMA	LOWE 1/3RD OF ESOPHJAGUS	-	B/929/23	NEGATIVE	NEGATIVE	PALLATIVE CHEMOTHERAPY			
27	MOHAN REDDY	60	MALE	KOALR	328032	66744	02/01/2024	07/02/2024	ESOPHAGUS	ADENOCARCINOMA	ADENOCARCINOMA	LOWER 1/3RD OF ESOPHAGUS	-	B/224/234	NEGATIVE	NEGATIVE	PALLATIVE CHEMOTERAPY			
28	VENKATAGIRIJAPPA	84	MALE	CHINTAMANI	277616	30091	10/09/2023	27/09/2023	ESOPHAGUS	SQUAMOUS CELL CARCINOMA	WELL DIFFRENTIATED	LOWER 1/3RD OF ESOPHAGUS	-	B/3144/23	NEGATIVE	NEGATIVE	DISTAL ESOPHAGECTOMY WITH GASTRIC PULLUP	30	2	NOT INVILVED
29	NAGAVENI	45	FEMALE	KOLAR	323021	22441	15/12/2023	30/12/2023	STOMACH	POORLY DIFFRENTIATED	POORLY DIFFRENTAITED	BODY OF STOMACH	-	B/4583/23	NEGATIVE	NEGATIVE	NEOADJUVENT CHEMOTHERAPY			
30	MANGALAMMA	70	FEMALE	MALUR	314893	21334	01/12/2023	10/12/2023	STOMACH	ADENOCARCINOMA	ADENOCARCINOMA	LESSER CURVATURE	-	B/4281/23	NEGATIVE	NEGATIVE	DEFAULTED TREATMENT			
31	RAMKRISHNA REDDY	68	MALE	KOLAR	374503	74221	15/03/2024	27/04/2024	ESOPHAGUS	SQUAMOUS CELL CARCINOMA	MODERATELY DIFFRENTIATED	MIDDLE 1/3RD OF ESOPHAGUS	-	B/1300/24	NEGATIVE	NEGATIVE	NEOADJUVENT CHEMOTHERAPY			
32	KRISHNAPPA	53	MALE	KOLAR	328874	75719	25/03/2024	06/04/2024	STOMACH	POORLY DIFFRENTIATED	ADENOCARCINOMA	FUNDUS	-	B/1736/24	NEGATIVE	NEGATIVE	PALLATIVE CHEMOTHERAPY			