# Comprehensive Review on Etiology, Diagnosis, and Management of Esophageal Malignancy: Unraveling Insights for Improved Patient Outcomes

Athalla Jeryco Julyando Putra[a], Rizka Fathoni Perdana[b*], Budi Widodo[c], Puguh Setyo Nughroho[b]

[a]Medical Study Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[b]Department of Otorhinolaryngology-Head and Neck Surgery, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[c]Department of Internal Medicine, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[*] Corresponding author: irmi-syafaah@fk.unair.ac.id

**Abstract**

Esophageal malignancy represents a formidable challenge in oncology due to its inherently fatal nature, marked by a remarkably low survival rate even with therapeutic interventions. This paper explores the intricate landscape of esophageal cancer, shedding light on the profound impact it has on patient outcomes and quality of life. Patients afflicted with lymph node involvement face a particularly grim prognosis, with a survival rate plummeting below 20% in the advanced stage of esophageal malignancy (Stage IV). Surgical interventions, while marginally enhancing survival rates, often introduce complications that further compromise the overall well-being of patients. This review underscores the pervasive pessimism in the prognosis of esophageal malignancy, frequently diagnosed at advanced stages. Despite notable progress in treatment modalities, the general prognosis remains suboptimal, reflecting the challenging clinical landscape. The last few decades have witnessed a surge in the incidence of esophageal malignancy, compounding the urgency for improved understanding and innovative therapeutic approaches. Notably, advancements in the treatment of esophageal malignancy have failed to yield significantly enhanced overall survival rates, with approximately 10% survival at the 5-year mark and varying between 15-45% for patients post-esophagectomy. This comprehensive exploration serves as a critical overview of the dire prognosis associated with esophageal malignancy, emphasizing the imperative for continued research and novel strategies to ameliorate outcomes in the face of this formidable oncological challenge.

Keywords: Esophageal malignancy, Cancer, Treatment.

## 1. Introduction

Esophageal cancer stands as a formidable adversary in the field of oncology, casting a long shadow over patients and healthcare providers alike. Its reputation as one of the most lethal malignancies is deeply entrenched in the intricate interplay of factors that span epidemiology, etiology, histopathology, and prognosis. Despite strides in medical science, the prognosis for esophageal cancer remains disheartening, necessitating an in-depth review to bridge existing gaps and pave the way for enhanced patient outcomes. The compelling imperative behind this review lies in the urgent need to comprehensively understand esophageal cancer, a disease characterized by its grim prognosis and limited treatment success. The global burden of esophageal cancer is substantial, ranking as the sixth leading cause of cancer-related deaths worldwide (American Cancer Society, 2020). This study is propelled by the critical necessity to delve into the

epidemiological intricacies of esophageal cancer, unravelling geographical variations in incidence rates and shedding light on disparities that demand targeted interventions.

The multifaceted etiology of esophageal cancer serves as another catalyst for this study. Lifestyle factors, including smoking, alcohol consumption, and dietary habits, play pivotal roles in the genesis of this malignancy (Huang and Yu, 2018). Moreover, the influence of age and environmental factors, such as the temperature of drinking water, adds layers of complexity that demand careful exploration. To advance our understanding, a nuanced review of these factors is indispensable for tailoring preventive strategies and implementing effective early detection measures. Histopathologically, esophageal cancer unveils itself in diverse subtypes, primarily squamous cell carcinoma and adenocarcinoma, each presenting unique challenges in diagnosis and treatment (American Cancer Society, 2020). Beyond these prevalent types, rarer variants like lymphoma, melanoma, or sarcoma also contribute to the complexity of esophageal cancer's histological landscape. This review endeavors to shed light on these less common variants, recognizing their significance in refining diagnostic precision.

The intricate relationship between esophageal cancer and the prognostic landscape adds another layer to the rationale behind this study. The prognosis for esophageal cancer is undeniably bleak, with survival rates plummeting, particularly in advanced stages. A stark illustration of this lies in the less than 20% survival rate for patients with Stage IV esophageal cancer, compounded by the fact that surgical interventions, while marginally improving survival, often introduce complications that compromise the patient's quality of life (Boiles and Babiker, 2021). Moreover, the escalating incidence of esophageal cancer over the past decades further underscores the urgency of this review. While advancements in therapeutic modalities have been made, the overall outlook remains unsatisfactory, with only approximately 10% of patients surviving five years post-diagnosis and 15-45% survival rates following esophagectomy (Huang and Yu, 2018).

In conclusion, this review embarks on a comprehensive exploration of esophageal cancer, aiming to dissect its complexities across epidemiology, etiology, histopathology, and prognosis. The study's impetus lies in the pressing need to decipher the intricacies of this formidable malignancy, with the ultimate goal of informing targeted interventions that can transform the current narrative and offer a glimmer of hope to those affected by esophageal cancer.

## 2. Review Content

### 2.1 Anatomy and Physiology of the Esophagus

The esophagus, also known as the gullet, is a muscular tube that extends from the pharynx to connect with the stomach. It is divided into three parts: cervical, thoracic, and abdominal. The cervical part starts from the cricopharyngeus muscle, approximately at the level of the 7th cervical vertebra, about 15 cm from the incisors, extending to the thoracic inlet around the level of the thoracic vertebra, 18 cm from the incisors. The cervical segment spans about 4-5 cm, bounded by the trachea in the front, vertebrae in the back, and carotid sheaths and thyroid gland laterally. The thoracic esophagus extends from the suprasternal notch to the diaphragmatic hiatus, starting at the thoracic inlet and continuing to the 10th-11th thoracic vertebra. The abdominal esophagus pierces the diaphragm at the right crus, reaching the cardia of the stomach at the level of the 10th thoracic vertebra and entering the stomach (Chaudry and Bordoni, 2021).

During the process of food entering the mouth, it mixes with saliva enzymes, transforming into a mass called bolus. Swallowing begins in the pharynx, involving the relaxation of the upper esophageal sphincter (UES) to allow the bolus to pass into the esophagus. Peristaltic contractions of esophageal muscles assist the bolus in moving towards the lower esophagus, triggering the relaxation of the lower esophageal sphincter (LES) for

entry into the stomach, initiating the digestion process. The esophagus has two high-pressure zones, the Upper Esophageal Sphincter (UES) and Lower Esophageal Sphincter (LES), preventing backflow of food. The UES is between the pharynx and the cervical esophagus, while the LES is at the junction of the esophagus and the stomach, serving as an anti-reflux barrier (Bajwa and Kasi, 2022). The blood supply to the cervical esophagus and the Upper Esophageal Sphincter (UES) comes from the inferior thyroid artery, while the thoracic esophagus receives blood from pairs of esophageal arteries originating from the aorta or terminal branches of the bronchial artery. The abdominal esophagus and the Lower Esophageal Sphincter (LES) are supplied by the left gastric artery and branches of the left phrenic artery (Chaudry and Bordoni, 2021). The esophagus is innervated by the sympathetic and parasympathetic nervous systems, primarily through the vagus nerve and the spinal cord. The vagus nerve is responsible for the parasympathetic motor function of esophageal muscles (Chaudry and Bordoni, 2021).

**2.2 Histology of the Esophagus**

The esophageal wall consists of three layers: mucosa, submucosa, muscularis propria (muscle), and fibrous tissue. Unlike other parts of the digestive tract, the esophagus lacks a serosal layer but has a thin outer layer of connective tissue. The mucosal layer includes stratified squamous epithelium, composed of three sub-layers: mucosal membrane, lamina propria, and muscularis mucosae (Yazaki and Sifrim, 2012). The muscularis propria of the esophagus has several layers, including circular muscles surrounded by longitudinal muscles. The cervical esophagus contains striated muscle, while the thoracic esophagus contains smooth muscle. The transition between the two muscle types occurs gradually, and there is a segment around 4-6 cm that contains a mixture of both. The lower esophagus only contains smooth muscle and is covered by a serosal layer (Yazaki and Sifrim, 2012).

**2.3 Esophageal Cancer**

Esophageal cancer is a malignancy affecting the esophagus, originating from the uncontrolled growth of cancerous cells in its layers (American Cancer Society, 2020). Almost any part of the human body can develop cancer, where cells grow and divide to form new cells in a regulated manner. When errors or damage occur in this process, abnormal cells can develop and proliferate, forming tumors or tissue masses. Tumors can be either malignant (cancerous) or benign. Malignant tumors, or cancer, can invade nearby tissues and spread to distant parts of the body to form new tumors (National Cancer Institute, 2021). Among gastrointestinal malignancies, esophageal cancer is one of the most aggressive types. It ranks sixth as a cause of death related to cancer in males, with an overall 5-year survival rate of only 15% - 25%. Esophageal cancer has two main histological subtypes: squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma (SCC) is more prevalent in East Asia, East and South Africa, and Southern Europe, while it is less common in North America and Northern Europe. SCC accounts for approximately 90% of cases in Japan (Watanabe, et al., 2020). The location of SCC is often in the upper and middle esophagus, whereas adenocarcinoma typically occurs in the lower thoracic esophagus, associated with conditions like Barrett's esophagus, leading to the replacement of squamous cells with glandular cells in the esophagus (American Cancer Society, 2020). Other rare types of esophageal cancer include lymphoma, melanoma, and sarcoma (Short et al., 2017).

**2.4 Etiology and Risk Factors**

There are several factors that can contribute to esophageal cancer, including a history of smoking, alcohol consumption, Gastroesophageal Reflux Disease (GERD), and the patient's diet and obesity history (Huang and Yu, 2018). Additionally, esophageal cancer is associated with advancing age (Ardhiansyah, 2019). Nearly 90% of patients with squamous cell carcinoma of the esophagus in the United States have a history of smoking and alcohol consumption (Boiles and Babiker, 2021). DNA and crucial genes that help protect against cancer cells are damaged by the abundant chemicals in tobacco. Substances damaging DNA include benzene, polonium-210, benzo(a)pyrene, and nitrosamines (Cancer Research UK, 2016). In developing

countries, it is not precisely known, but there is a possibility that patients may have poor nutrition, infrequent consumption of fruits and vegetables, and high-temperature drinking water (Boiles and Babiker, 2021). For example, in Japan, a Prospective Study based on the Japanese Public Health Center showed an 11% reduction in squamous cell carcinoma of the esophagus, attributed to a 100-gram per day increase in fruit and vegetable consumption. In contrast, in China, where malnutrition is prevalent and there is a deficiency of selenium, zinc, folate, riboflavin, and vitamins A, C, E, and B12, there is a strong association with the incidence of squamous cell carcinoma of the esophagus (Epidemiol, 2013).

Individuals with obesity (BMI > 40) have a twice as high risk and are proven to be a contributing factor to the occurrence of esophageal adenocarcinoma. This association remains evident regardless of the presence of GERD symptoms in obese patients when compared to individuals with a BMI < 25. Obese patients are more likely to experience Gastroesophageal Reflux Disease (GERD) and the development of Barrett's esophagus, increasing the likelihood of esophageal cancer (Uhlenhopp et al., 2020). Esophageal cancer, predominantly comprising squamous cell carcinoma and adenocarcinoma, is a widely observed malignancy worldwide. One risk factor for this cancer is Human Papillomavirus (HPV) infection, associated with squamous cell carcinoma, although the incidence caused by this virus is relatively low (Abnet et al., 2017). Furthermore, periodontal microbiota infection is considered a potential risk factor for esophageal cancer in research. Microbiota infections such as Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia are evaluated as contributors to esophageal malignancy (Kawasaki et al., 2020).

**2.5 Pathogenesis**

The mechanism of cancer development involves a process called carcinogenesis. Carcinogenesis is an event that includes the procedure of forming malignancy or cancerous diseases, which doesn't occur directly but, if left to accumulate, can cause damage to the body. There are three stages in carcinogenesis:

1. Initiation

In this stage, the initial action of carcinogenic compounds takes place. Carcinogenic compounds are substances that cause the development of malignancy. These compounds can alter the functional DNA structure or different genes, usually referred to as gene mutations. Carcinogenic compounds are commonly found in chemical substances in food, beverages, drugs, the environment, UV rays, gamma rays, and air pollution.

2. Promotion

The next stage involves cell proliferation or the cell division cycle containing genes that have mutated due to carcinogenic substances. The mutated genes form groups (clones) within the body. Activation of protein kinase C (PKC) occurs in this stage, resulting in the phosphorylation of proteins that regulate cell differentiation or proliferation.

3. Progression

The final stage of carcinogenesis is progression, where there is a rapid division of cancer cells and the cells move (invasion) from the original location to other sites, known as metastasis. This stage is characterized by the emergence of angiogenesis, the formation of new blood vessels, which is abnormal.

**2.6 Diagnosis**

Screening for esophageal cancer can utilize Esophago-gastro-duodenoscopy (EGD) as the gold standard examination. The screening aims to detect the presence of Barrett's Esophagus (BE) and dysplasia or the development of abnormal cells that occur in squamous epithelium, indicating esophageal malignancy (di Pietro et al., 2018). Another screening method can also be done with endoscopy, which is recommended for

diagnosing patients with malignancy symptoms (Kim and Shah, 2017). For the treatment or therapy of patients with esophageal cancer to succeed, various accurate and thorough diagnoses are required. Diagnosis of malignancy depends on signs and symptoms in patients, medical history, age, and other conditions. An approach with patient anamnesis is needed to gather data, useful for obtaining the patient's disease history and habits, which are risk factors for malignancy, such as smoking, alcohol consumption, and others. Physical examination will be conducted after anamnesis, including inspection and palpation. Palpation around the neck is performed to check for masses in the esophagus, and examination of gland enlargement is also necessary to assess the patient's status. If malignancy is suspected, further examinations or diagnostic tests, including esophageal biopsy, may be conducted, and the patient may be referred to an internal medicine specialist for further examination. Supportive examinations include complete blood count, blood chemistry, liver function test, barium swallow test, CT-scan / PET scan and MRI, and endoscopy (upper endoscopy, endoscopic ultrasonography, bronchoscopy, thoracoscopy, and laparoscopy)

Various supportive tests for diagnosing esophageal malignancy aim to identify areas of malignancy, determine the presence of metastasis and the extent of metastasis, assist in determining appropriate treatment and therapy for patients, and explore the possibility of secondary cancer or recurrence after treatment (American Cancer Society, 2020). Staging is also part of the diagnostic phase as it plays a crucial role in determining the appropriate management, treatment, and therapy for patients (Indarti and Sekarutami, 2013).

**2.7 Staging**

Determining the stage of esophageal malignancy is assessed using the TNM system developed by the American Joint Committee on Cancer (AJCC). Accurately determining the stage and severity before treatment can influence the overall prognosis, therapy, and treatment. The TNM system stands for tumor, node, metastasis, using a combination of letters and numbers. Stage T refers to the identification of the depth of primary tumor invasion or the size and extent of the primary tumor. Stage N is defined by whether there is involvement with periesophageal lymph nodes. Stage M is defined as whether there is spread (metastasis) or not, and distant metastasis (Napier et al., 2014). Determining the stage categories of esophageal malignancy and establishing clinical and pathological stage groups involves different analyses. Clinical stage (cTNM) is considered less accurate because it is based on pre-treatment, clinical, radiological, and other investigations without resection processes, leading to pathological stage (pTNM) being based on post-surgery, histopathology, and other pathological examinations, serving as the basis for all cancer stages. According to the American Joint Council on Cancer (AJCC) 8th edition, as performed below (Rice et al., 2017). Grading (G) or assessing the degree of malignancy is also a factor that affects the treatment given. By classifying cancer cells based on their rate of development and the appearance of the cancerous cell formation itself. If cancer cells appear normal and the growth is slow, they are categorized as low grade, whereas they are categorized as high grade if cancer cells appear highly abnormal, and the growth or development is rapid (Rice et al., 2017).

**2.8 Management**

The therapy or treatment for esophageal malignancy is determined by the stage of malignancy, histopathological findings, and the patient's condition. Some treatments that can be provided include surgery, endoscopic therapy, radiation therapy, chemotherapy, and immunotherapy (Watanabe et al., 2020). Surgery is the gold standard for treating cancer or malignancy at an early stage (Barret and Prat, 2018). Tumors found at stage 0 contain abnormal cells called high-grade dysplasia, a type of precancerous condition. Treatment options include endoscopy such as photodynamic therapy, radiofrequency ablation, or endoscopic mucosal resection. Surgery, specifically esophagectomy, may also be performed to remove the abnormal part of the esophagus. Next is stage 1 (T1a) tumor located in the mucosa but not extending into the submucosa. In this stage, the tumor grows within several layers of the esophageal wall but has not reached the lymph nodes or

surrounding organs. Healthy and willing patients may undergo esophagectomy. Chemotherapy and radiation therapy (chemoradiation) are recommended if there is suspicion that the malignancy has not been completely removed after surgery (Berry, 2014). In the treatment of stage 2 (T2), the approach varies if the cancer or malignancy begins to invade the muscularis propria. Although at stage 2, malignancy grows in the main muscle layer of the esophagus and spreads to the lymph nodes. Usually, chemoradiation is performed before surgery or surgery is performed directly if the tumor is less than 2 cm (Boiles and Babiker, 2021). In certain conditions, if malignancy is located in the abdominal part of the esophagus, chemotherapy without radiation may be performed before surgery. However, if malignancy is located in the upper part of the esophagus, chemoradiation becomes the primary treatment. For stage 3 treatment, chemoradiation is given followed by surgery, but patients with adenocarcinoma-type malignancy located in the lower esophagus are given chemotherapy with radiation before surgery. Surgery alone can be performed for some small tumors. In the case of malignancy in the upper esophagus, primary treatment recommended is chemoradiation instead of surgical procedures. However, patients who do not undergo surgery must be monitored with an endoscopic approach to ensure the possibility of any remaining malignancy (Wolf et al., 2011). Combination chemotherapy and immunotherapy are given if chemoradiation is not feasible for malignancy that is too large for surgery. To treat stage 4 malignancy in a very advanced position where malignancy has invaded lymph nodes and metastasis has occurred, surgery is no longer the primary treatment at this stage. Treatment aims to control malignancy as much as possible and alleviate symptoms in patients. Chemotherapy is administered along with targeted drug therapy or immunotherapy. For pain or difficulty swallowing, patients are usually given radiation therapy. Drugs such as larotrectinib or entrectinib are options (Makino et al., 2018).

### 2.9 Prognosis

Esophageal malignancy is one of the deadliest cancers, characterized by a very low survival rate, even with treatment. Many patients experience complications leading to a poor quality of life. Patients with lymph node involvement see a decreased survival rate, with less than 20% survival for those in stage IV esophageal malignancy. Despite a slight improvement in survival with surgical treatment, complications post-surgery often worsen the patients' quality of life (Boiles and Babiker, 2021). Overall, the prognosis for esophageal malignancy remains grim, commonly diagnosed at advanced stages. Despite advancements in treatment, the general outcomes are still suboptimal, with approximately 10% survival at 5 years and around 15-45% survival for patients post-esophagectomy (Huang and Yu, 2018).

## 3. Conclusion

In conclusion, this comprehensive review explain the intricate facets of esophageal cancer, spanning epidemiology, etiology, histopathology, and prognosis. By dissecting the complexities of this formidable malignancy, we underscore the urgent need for targeted interventions. The grim prognosis, coupled with limited treatment success, emphasizes the critical importance of refining preventive strategies, implementing early detection measures, and advancing therapeutic modalities. As esophageal cancer continues to exact a heavy toll globally, this review serves as a clarion call for sustained research efforts, interdisciplinary collaboration, and innovative approaches to shift the paradigm, offering renewed hope and improved outcomes for those grappling with this challenging disease.

## Acknowledgements

The authors would like to thank all the supervisors, enabling the successful implementation of this study.

## References

Abnet, C. C., Arnold, M., & Wei, W. Q. 2018. Epidemiology of esophageal squamous cellcarcinoma. Gastroenterology, 154(2), 360-373.doi: 10.1053/j.gastro.2017.08.023

American Cancer Society. 2020. About EsophagusCancer. Tersedia di:https://www.cancer.org/cancer/esophagus-cancer/about.html [Diakses 27 Juni 2022].

Ardhiansyah, A. O. 2019. Deteksi Dini Kanker. Surabaya: Airlangga University Press. Arnal, M.J. D., Arenas, Á. F., & Arbeloa, Á. L. 2015.Esophageal cancer: Risk factors, screening, andendoscopic treatment in Western and Eastern countries. World J Gastroenterol, 21(26), 7933-7943. doi: 10.3748/wjg.v21.i26.7933

Bajwa SA, Toro F, Kasi A. Physiology, Esophagus. 2022. In: StatPearls [Internet]. Treasure Island(FL): StatPearls Publishing; 2022 Jan-. Availablefrom:https://www.ncbi.nlm.nih.gov/books/NBK519011/

Barret, M., & Prat, F. 2018. Diagnosis and treatment ofsuperficial esophageal cancer. Ann Gastroenterol, 31(3), 256-265. doi: 10.20524/aog.2018.0252

Berry, M. F. 2014. Esophageal cancer: Staging system and guidelines for staging and treatment. JThorac Dis, 6(Suppl 3), S289-97. doi:10.3978/j.issn.2072- 1439.2014.03.11

Chaudhry SR, Bordoni B. Anatomy, Thorax,Esophagus. 2021. In: StatPearls [Internet].Treasure Island (FL): StatPearls Publishing; 2022Jan-. Available from:https://www.ncbi.nlm.nih.gov/books/NBK482513/

di Pietro, M., Canto, M. I., & Fitzgerald, R. C. 2018. Clinical endoscopic management of earlyadenocarcinoma and squamous cell carcinoma ofthe esophagus: Screening, diagnosis, and therapy.Gastroenterology, 154(2), 421-436. doi:10.1053/j.gastro.2017.07.041

Huang, S.H., Wu, I.C., Wu, D.C., Wu, C.C., Yang, J.F., Chen, Y.K., Chai, C.Y., Chiu, Y.W., Huang, C.T., Lee, T.C. and Wu, M.T., 2012. Occupational risks of esophageal cancer in Taiwanese men. The Kaohsiung journal of medical sciences, 28(12), pp.654-659.

Huang, F. L., & Yu, S. J. 2018. Esophageal cancer: Risk factors, genetic association, and treatment.Asian Journal of Surgery, 41(3), 210–215. doi:https://doi.org/10.1016/j.asjsur.2016.10.005

Indarti, A. F., & Sekarutami, S. M. 2013. Tatalaksana radiasi pada kanker esofagus. Radioterapi &Onkologi Indonesia, 4(2), 70-76. Tersedia di:http://www.pori.or.id/journal/index.php/JORI/article/view/18/15 [Accesed 29 Juni 2022].

Kawasaki, M., Ikeda, Y., Ikeda, E., Takahashi, M.,Tanaka, D., Nakajima, Y., Arakawa, S., Izumi, Y., & Miyake, S. 2020. Oral infectious bacteria in dental plaque and saliva as risk factors in patients with esophageal cancer. Cancer, 127(4), 512-519. doi: 10.1002/cncr.33316

Kim, J. A., & Shah, P. M. 2017. Screening and prevention strategies and endoscopic managementof early esophageal cancer. Chin Clin Oncol, 6(5),50. doi: 10.21037/cco.2017.09.05

Makino, T., Yamasaki, M., Tanaka, K., Miyazaki, Y., Takahashi, T., Kurokawa, Y., Motoori, M.,Kimura, Y., Nakajima, K., Mori, M., & Doki, Y.2018. Treatment and clinical outcome of clinicalT4 esophageal cancer: A systematic review. AnnGastroenterol Surg, 3(2), 169-180. doi:10.1002/ags3.12222

Napier, K. J., Scheerer, M., & Misra, S. 2014.Esophageal cancer: A review of epidemiology,pathogenesis, staging workup, and treatmentmodalities. World J Gastrointest Oncol, 6(5), 112-20. doi: 10.4251/wjgo.v6.i5.112

National Cancer Institute. 2021. What Is Cancer?.Tersedia di: https://www.cancer.gov/about-cancer/understanding/what-is-cancer [Diakses 29Juni 2022].

Rice, T. W., Patil, D. T., & Blackstone, E. H. 2017. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: Application to clinical practice. AnnCardiothorac Surg, 6(2), 119-130. doi:10.21037/acs.2017.03.14

Shah, I.A., Bhat, G.A., Rafiq, R., Nissa, N., Muzaffar, M., Rasool, M.T., Lone, M.M., Lone, G.N., Boffetta, P. and Dar, N.A., 2019. Strenuous occupational physical activity: Potential association with esophageal squamous cell carcinoma risk. Proceedings of Singapore Healthcare, 28(4), pp.232-242.

Short, M. W., Burgers, K. G., Fry, V. T. 2017. Esophageal cancer. Am Fam Physician, 95(1), 22-28. PMID: 28075104

Uhlenhopp, D. J., Then, E. O., Sunkara, T., & Gaduputi, V. 2020. Epidemiology of esophageal cancer: Update in global trends, etiology, and risk factors. Clin J Gastroenterol, 13(6), 1010-1021.doi: 10.1007/s12328-020-01237-x

Watanabe, M., Otake, R., Kozuki, R., Toihata, T., Takahashi, K., Okamura, A., & Imamura, Y. 2020. Recent progress in multidisciplinary treatment for patients with esophageal cancer. Surg Today, 50(1), 12-20. doi: 10.1007/s00595-019- 01878-7

Wolf, M. C., Stahl, M., Krause, B. J., Bonavina, L.,Bruns, C., Belka, C., & Zehentmayr,

Yazaki, E., & Sifrim, D. 2012. Anatomy andphysiology of the esophageal body. Diseases of the Esophagus, 25(4), 292-298.