Proceedings of ICMMGH 2025 Workshop: Computational Modelling in Biology and Medicine
DOI: 10.54254/2753-8818/90/2025.GU20968

The Pathogenesis and Therapy Progress of Esophageal Cancer

Jinchen Han[1,a,*]

[1]*Annie Wright Schools, Tacoma, 98403, United States*
a. jinchen_han@aw.org
**corresponding author*

Abstract: Esophageal cancer (EC) is a devastating cancer well known for its aggressive nature, limited treatment options, and poor prognosis. It spreads out the world through two of its subtypes, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), creating high global incidence and mortality. In recent years, studies and research have been done to explore the molecular mechanisms and multiple treatments. This paper provides a comprehensive overview of EC, going through the risk factors and high-incidence areas of ESCC and EAC respectively; it discusses the molecular mechanisms underlying EC development, highlighting several key signaling pathways, as well as the critical role of some ribosomal protein drivers and biomarkers played in the prediction and development of EC. The paper also aims to determine the central causes of death in EC, metastasis, and its mechanism. Lastly, this review examines and demonstrates the modern therapeutic approaches of EC, especially the combination of immunotherapy with other therapies. By synthesizing recent research and therapeutic developments, this study contributes to the ongoing campaign of EC, laying the foundation for more effective clinical interventions and improved patient outcomes in the future.

Keywords: Esophageal cancer(EC), esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma (EAC), Immune Checkpoint Inhibitors (ICIs).

1. Introduction

In recent years, esophageal cancer (EC) has drawn a significant amount of attention, it has long been one of the most difficult cancers medicine is trying to conquer, as the sixth most common cause of cancer-related mortality worldwide, and the seventh most common cancer worldwide, EC's aggressive nature of late-stage detection, poor prognosis, high recurrence rate, and high rate of metastasis make it difficult to treat even though the medicine has targeted it so much. Moreover, EC patients have a limited survival benefit with a median overall survival of fewer than 10 months, and an overall 5-year survival rate of approximately 20%, which means 1 in every 20 cancer deaths, in some regions the survival rate is less than 5%, only ~15–40% even post esophagectomy, therefore, EC is responsible for over 500,000 deaths annually [1-3].

As the progression in molecular biology and medical chemistry, the understanding of the pathogenesis of EC has deepened and some key molecular drivers of EC have been exposed to the medical field. Therapeutic approaches have emerged following those discoveries targeting EC; first from the earliest attempt at EC surgery which is the esophagectomy, often accompanied by all kinds

© 2025 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/90/2025.GU20968

of complications, observed poor prognosis, and high recurrence rate. However, although improved therapy of minimally invasive esophagectomy (MIE) that reduced morbidity has emerged, it's still lacking in practicality(most esophageal cancer patients have already locally advanced or metastatic disease when they are aware of any symptoms) [4,5]. Later is radiotherapy, hardly effective and usually brings up more problems in surrounding tissues such as radiation-induced esophageal cancer (RIEC) [6]. Chemotherapy emerged in recent decades but is also limited in efficiency, causing systemic toxicity, nowadays, it often combines with other therapies to achieve better efficiency and reduced side effects. Lastly and most recently, targeted therapy and immune therapy have taken the dominant place in EC treatment, especially their combination with chemotherapy, continuing to improve the efficiency of EC treatment and patient survival, laying the foundation for more effective treatment options for EC.

This paper will provide a comprehensive overview of the pathogenesis and therapeutic progress of EC, it'll go through the high-incidence regions, analyze potential risk factors, encompass molecular underpinnings of the development of the disease, illuminate the role of some key genetic alterations, and uncover the mechanisms of metastasis. Moreover, the paper will also conclude and examine all the therapeutic approaches in recent years, especially the integration and combination of these therapies, in addition to that, the role of biomarkers will also be mentioned in this paper to intensify the research in the crucial prognosis and treatment response predictions. Through these topics, this paper will contribute to the ongoing efforts to combat EC, both in basic research and clinical practice; by understanding the complex mechanisms that induce EC and utilizing the best combination of treatments, the prognosis of patients around the world can be changed, and there is hope that this devastating disease can be effectively controlled in the future.

2. Pathology/Pathogenesis of esophageal

2.1. Regions of high incidence and risk factors

There are two predominant histological subtypes of EC, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC accounts for about 90% of the 456,000 incidents of EC each year, and EAC accounts for another 10% but EAC incidents are increasing in recent years [7]. ESCC is highly prevalent in Eastern to central Asia and eastern to southern Africa (The highest incidence of ESCC starts from East Asia to Central Asia, with another band extending along the Great Rift Valley to the Indian Ocean coast of Africa, Uruguay and the surrounding area in South America have the third highest incidence of ESCC around the world) with the two leading countries China and Japan, lower incidence rates in North America and other parts of Europe, where EAC is more prevalent [5,7].

EC is unique, the prevalence in different regions is quite significant; the proportion of the two subtypes of esophageal cancer ESCC and EAC varies greatly from country to country; and the difference between different countries is more than 10 times [7]. Racial and ethnic differences have been closely associated with the prevalence of EC, the risk of EAC in Caucasians is twice that of Hispanics and 3-4 times that of blacks [5]. The prevalence of Barrett's esophagus (metaplasia from normal squamous mucosa to columnar endometrium of the esophagus, is the only known precancerous lesion of EAC in non-Hispanic whites, the presence of it can increase the risk of EAC by 30 to 40 times in prevalence) was 6.1% among non-Hispanic whites, 1.7% among Hispanics, and 1.6% among blacks [5,7]. The reasons for these large differences are unknown, and the currently known risk factors cannot be fully explained, as there is a gap in research on EC, and can be a potential future direction. Studies in recent years have also revealed a substantial increase in the risk of EAC in people over the age of 50 [5]. Moreover, gender contributes significantly to the risk of EC. The

DOI: 10.54254/2753-8818/90/2025.GU20968

ratio of male to female patients with Barrett's esophagus is about 2:1, and the incidence of EAC in males is 38 times higher than in females [5].

What's notable about ESCC is that its prevalence is significantly more than double that of whites and blacks, which is contrary to the EAC [7]. ESCC not only varies significantly among countries but also within countries, especially in China; the incidence of ESCC in China varies by 10 times, and the difference between short geographical distances is remarkable. In some small areas of China, EC (mainly ESCC) has even become the primary cause of death, and the huge population of China also makes it account for half of all EC cases in the world [7]. Overall, ESCC is more common in nonindustrialized countries, and EAC is the predominant esophageal cancer in developed nations [4,8].

The difference reflects the etiology of EC, the risk factors of EC emphasize influences of different lifestyles, environments, and socioeconomic. The ESCC incidence rate is remarkably higher for those who consume an average of more than 170g of alcohol per week, the gene mutation induced by acetaldehyde is one of the crucial causes of ESCC; the threshold is even lower for women, as an average of more than 70g of alcohol per week will be enough to increase the risk of women to get ESCC or deterioration [5]. Moreover, tobacco consumption and smoking are also closely correlated to ESCC, exhibiting an increase in risk, especially in the case of men. Low body mass index(BMI) contributes to the ESCC as well, a higher BMI leads to a lower risk of ESCC, but poor nutrients, famine, and food rich in carcinogens are still the problems of most unindustrialized and developing countries [5]. Studies in animal models of ESCC have shown that high-temperature water and food can enhance the action of chemical carcinogens through thermal stimulation [7]. Lastly, as is the case for most unindustrialized and developing countries, poor medical conditions and limited access to healthcare, especially for people with relatively low socioeconomic; poor oral conditions, and Human papillomavirus (HPV) related to this phenomenon contribute a lot to the higher incidence in these countries [5,7]. Noting that almost all of these risk factors of ESCC are more prominent in nonindustrialized countries or developing countries. This explains the geographic and the driven factor difference between ESCC and EAC.

Some risk factors are more often observed in developed countries that contribute to the EAC, including obesity, similar to risk factors of ESCC, which causes a higher risk for EAC; Barrett's esophagus as it is often seen as the early phase of the EAC; unhealthy diets that are high in fat and sugar but low in vegetable and fruits leads to a higher chance of getting Barrett's esophagus and EAC(especially in the United States); gastroesophageal reflux disease (GERD), patients with GERD have a risk of getting EAC five times more than that of a normal person; smoking and alcohol drinking also play a role but not as significant as in the case of ESCC [5,7].

2.2. Ribosomal Protein S15(RPS15)

It is important to understand ribosomes in order to study the molecular mechanism of EC(especially ESCC) due to the level of its protein correlates closely with cell growth rate(standards of many cancers). Dedicated studies and experiments have shown that RPS15 is a significant molecular driver of EC, and it correlates to the poor prognosis of EC. RPS15 promotes ESCC cell metastasis and proliferation, both in vitro and in vivo, it also significantly increases lymph node metastasis [9]. These studies suggest that the expression of RPS15 in EC is a potentially significant target, which means inhibitors or therapeutic regimens that inhibit the growth of RPS15 overexpressing cells are likely feasible, such as folic acid(a small molecule, also known as folate or vitamin B9) that has been shown to have a therapeutic effect on ESCC [9]. The relationship between RPS15 and the two oncogenic signaling pathways, the Wnt/β-catenin signaling pathway and NOTCH signaling pathway which will be discussed in detail later, is still unclear, further research and study can also focus on this.

DOI: 10.54254/2753-8818/90/2025.GU20968

2.3. Wnt/β-catenin Signaling Pathway

The dysregulation of microRNA(miRNAs), small RNAs regulate the expression of tumor suppressor genes and oncogenes and are involved in almost all tumor-related processes, go through specific signaling pathways, Wnt/β-catenin signaling pathway is an important one to understand in the case of EC. Mutations or overexpression of Wnt ligands and β-catenin lead to the accumulation of β-catenin in the nucleus, driving the expression of oncogenic target genes and epithelial-mesenchymal transformation (EMT) in ESCC cells [10]. Moreover, the Wnt/β-catenin signaling pathway also mediated MiR-221-induced chemical resistance [10]. These disorders promote cell proliferation, migration, and invasion, leading tumors to grow, metastasize, and become resistant to treatment.

Targeting the Wnt/β-catenin pathway with small molecule inhibitors or monoclonal antibodies has shown preclinical promise; the potential of the Wnt/β-catenin pathway as a tumor therapeutic target has been demonstrated, but more research is still needed to elucidate the molecular mechanisms of novel combination therapies targeting the Wnt pathway [10].

2.4. NOTCH Signaling Pathway

Other than the Wnt/β-catenin signaling pathway, the NOTCH signaling pathway is another significant signaling pathway that correlates with EC. The NOTCH signaling pathway regulates squamous differentiation of the skin and esophagus and determines tissue homeostasis; the dysregulation of the NOTCH signaling pathway can inhibit the squamous differentiation of the esophageal squamous skin cells, inducing oncogenic effects or further enhancements [11]. Through recent studies, NOTCH mutations are common in human EC, this closely relates to the risk factors of EC mentioned, such as gastroesophageal reflux, alcohol drinking, and inflammation [11]. In addition, normal esophageal epithelial cells are more vulnerable to this mutation than other skin cells. However, there is a dual role of the NOTCH mutation or disorder, it can also suppress tumors, depending on cell context and tumor type, revealing the complexity of the NOTCH signaling pathway, especially in the esophagus and the case of EC [11]. NOTCH activators may be used to prevent ESCC. Still, more studies are needed to illuminate the complex role of the NOTCH signaling pathway in the pathogenesis of EC and verify the clinical efficiency of NOTCH activators.

2.5. Ubiquitin-protein Ligase E3A (UBE3A)

UBE3A is a ubiquitin ligase involved in protein degradation. In research, the expression level of UBE3A in esophageal cancer tissues was abnormally elevated, and overexpression of UBE3A promoted the proliferation and invasion of esophageal cancer cells in vitro, which proved that UBE3A was the cause of the progression of esophageal cancer cells [12]. A potential therapeutic approach might be the inhibitor targeting the UBE3A.

2.6. Mechanism of Metastasis

Metastasis explains the invasiveness of EC, only by understanding its mechanism can we better plan the treatment in the clinic. Metastasis is the main cause of death in EC patients, and it greatly hinders the recovery of EC patients through several process steps, including local invasion, endoscopy, blood circulation, exosmosis, and distant colonization [13]. The metastasis mechanisms of EC are mainly divided into direct diffusion metastasis, hematogenous metastasis, and lymphatic metastasis [13]. Direct diffusion and metastasis occur after the tumor breaks through the loose outer membrane and invades adjacent tissues; blood-borne metastasis is usually secondary to lymph node metastasis and spreads to distant organs such as the lung and liver; lymphatic metastasis is the most important factor affecting prognosis [13].

DOI: 10.54254/2753-8818/90/2025.GU20968

Multiple molecular mechanisms play a role in metastasis, including cytokines, specific proteins, and tumor-associated cells; they shape the metastasis microenvironment. Cytokines such as VEGF and EGF facilitate the entry of tumor cells into the blood circulation by promoting angiogenesis and lymphangiogenesis [13]. VEGF-A and VEGF-B indirectly aid tumor spread by binding to VEGFR-1 and VEGFR-2, enhancing vascular permeability and activating downstream signaling pathways [13]. CC chemokines promote immune escape by attracting immune cells such as regulatory T cells (Tregs) and Th17, further contributing to tumor progression [13]. Furthermore, matrix metalloproteinases (MMP) also play an important role in EC metastasis; they contribute to tumor cell exosmosis and microvascular basement membrane degradation by degrading extracellular matrix (ECM) and disrupting intercellular adhesion [13]. Lastly, tumor cells that enter the bloodstream called Circulating tumor cells (CTCS) can be used as an important indicator to diagnose distant metastases and help assess disease progression [13]. Together, these complex molecular and cellular mechanisms explain the highly aggressive nature of esophageal cancer, which is often metastatic at the time of diagnosis, making surgical treatment meaningless and other therapies hard to approach.

3. Treatment

Because of the often impracticality of surgical EC resection, this paper will mainly focus on modern approaches of immunotherapy and some combination therapies that cover chemotherapy.

3.1. Immunotherapy

Immunotherapy is a milestone in the entire history of EC treatment, with chemotherapy and target therapy, they become the most prevalent therapeutic approach to aggressive EC today.

3.1.1. ICIs

Immune checkpoint inhibitors (ICIs) are the cornerstone of immunotherapy, it completely alters the therapeutic mode of EC. One example of ICIs is the programmed cell death 1 (PD-1) inhibitor, it is an inhibitory receptor that is expressed on the surface of activated lymphocytes, and its ligands PD-L1 and PD-L2 are expressed on the surface of tumor cells, while cancer cells use the PD-1/PD-L1 and PD-1/PD-L2 pathways to create an immunosuppressive environmentp [1]. At this time, these ICIs can activate the immune response induced by anti-tumor T cells and inhibit both pathways to prevent overexpression of those two pathways [1]. Furthermore, ICIs are predicted to be able to address the universal problem of poor prognosis that closely correlates to most EC therapies; this prediction is based on the fact that patients with EC and high PD-L1 expression are poor, and ICIs target the PD-L1 and ESCC, a positive respond is looking forward [1]. There are three main clinical trials with ICI monotherapy: Pembrolizumab, Nivolumab, and Tislelizumab. Trials KEYNOTE-180 and 181, ATTRACTION-1 and 3, and RATIONALE-302 analyzed, evaluated, and contrasted those three ICI monotherapies with other traditional therapies, respectively.

Pembrolizumab is a recombinant human immunoglobulin monoclonal anti-PD-1 antibody; in the clinic, Pembrolizumab allows patients to obtain a longer median overall survival than traditional chemotherapy, especially for ESCC patients [1]. In 2019, Pembrolizumab was approved by the US Food and Drug Administration (FDA) as second-line therapy for advanced ESCC in patients with a combined positive score(CPS) greater or equal to 10 [1].

Nivolumab is a humanized immunoglobulin monoclonal anti-PD-1 antibody; under a specified condition such as for patients with advanced squamous cell carcinoma who have previously received fluoropyrimidine and platinum-based chemotherapy, Nivolumab improves the median overall survival of the patients, demonstrating a more effective treatment than standard chemotherapy [1]. In 2020, the FDA approved Nivolumab for patients with esophageal squamous cell carcinoma who had

DOI: 10.54254/2753-8818/90/2025.GU20968

previously received fluoropyrimidine and platinum-based chemotherapy, regardless of PD-L1 expression status [1].

Tislelizumab is a humanized immunoglobulin monoclonal anti-PD-1 antibody developed in China and is known for its good antitumor activity. In all patients and patients with tumor area positivity(TAP) scores ≥10%, Tislelizumab has a longer overall survival and better overall response rate than chemotherapy [1].

All three PD-1 inhibitors have shown remarkable efficacy in EC therapy, highlighting their survival benefits over traditional chemotherapy, and this efficacy can even be further magnified with combined therapy which will be discussed in detail later.

3.1.2. Serum proteins

While immunotherapy significantly improved patients' overall survival and response, promoting the treatment of EC, predictive biomarkers with practical applications are required to predict prognosis and treatment response in patients with EC immunotherapy and to evaluate risk and follow-up treatment options. In recent studies, three types of serum proteins associated with angiogenesis (Factors related to angiogenesis may be a possible cause of poor prognosis in patients with EC) among the many protein biomarkers are IL-8, TIE2, and HGF; they closely correlate to the overall survival and prognosis of the EC patients [2]. IL-8 induces neutrophil degranulation and enhances the growth and metastasis of tumor cells, which is very important in exploring the reasons for the poor effect of ICI [2]. TIE-2 regulates tumor angiogenesis and metastasis [2]. HGF activates mitosis, morphogenesis, and angiogenesis, while abnormal activation of HGF is one of the biggest contributors to the poor prognosis of EC treatment [2]. The monitoring of these proteins will predict the response of the immunotherapy for EC, allowing better stratification of patients of immunotherapy and minimizing unnecessary side effects while obtaining a better outcome.

3.2. Combination therapy

Because of the complex, aggressive, and resistant nature of EC, multidisciplinary intervention is required, making combined therapy to be the central treatment for EC today. Combination therapy maximizes the efficacy, minimizing side effects and recurrence, improving the overall survival of EC patients.

ICIs are increasingly being combined with other therapeutic modalities to maximize their efficacy, ICIs combined with targeted therapy, such as ICI combined with tyrosine kinase inhibitor (TKI), and radiotherapy show effects of significantly longer overall survival, improved pathologic complete response (pCR), and manageable safety. Immunotherapy combined with chemotherapy is also one of the effective combination therapy. Chemotherapy can improve the immunogenicity of tumors by inducing immunogenic cell death, releasing tumor antigens, and enhancing immune activation. Immunotherapy, when combined with chemotherapy, can reveal an even stronger anti-tumor effect. In the Phase II NIC-ESCC2019 trial, Camrelizumab(a PD-1 ICI) combined with chemotherapy showed a PCR rate of 31.4% and manageable safety [1]. The benefit of the combination of ICI with other therapy is even greater in the case of Pembrolizumab plus neoadjuvant CRT (carboplatin plus paclitaxel with RT) [1]. In the Phase I PALACE-1 trial, a high pCR rate of 55.6% and manageable safety are obtained, proving the effectiveness of immunotherapy combinations, and letting EC patients have better survival benefits [1,3,8].

4. Conclusion

With decades of efforts in the medical field, Esophageal cancer has progressively become less lethal, but it is still one of the most challenging cancers to treat; its late-stage detection, limited treatment

DOI: 10.54254/2753-8818/90/2025.GU20968

options, and aggressive nature allow it to stand out from various cancers. The prevention of EC is in daily life, unhealthy habits and bad social environment are the biggest contributors to EC. In recent years, the molecular basis of EC and a variety of therapeutic strategies have been deeply explored. Studies on molecular drivers such as RPS15 and UBE3A, as well as the learning of Wnt/β-catenin and NOTCH signaling pathways have laid the foundation and direction for various therapeutic programs, providing potential therapeutic targets and insights. Today's EC-targeting therapies, led by immunotherapy, particularly ICIs, have revolutionized the therapeutic landscape, offering significant survival benefits that are even more pronounced when combined with chemotherapy or other targeted therapies. In the future, research and studies should focus on personalized and multidisciplinary therapy approaches, targeting early diagnosis and better prevention, especially in the context of the complex interplay of habit, genetic, environmental, and socioeconomic factors contributing to EC.

References

[1] *Nagata, Y., Yamamoto, S., & Kato, K. (2022). Immune checkpoint inhibitors in esophageal cancer: Clinical development and perspectives. Human Vaccines & Immunotherapeutics, 18(6), 2143177.*

[2] *Gao, M., Wu, X., Jiao, X., Hu, Y., Wang, Y., Zhuo, N., Dong, F., Wang, Y., Wang, F., Cao, Y., Liu, C., Li, J., Shen, L., Zhang, H., & Lu, Z. (2024). Prognostic and predictive value of angiogenesis-associated serum proteins for immunotherapy in esophageal cancer. Journal for Immunotherapy of Cancer, 12(2), e006616.*

[3] *Ge, F., Huo, Z., Cai, X., Hu, Q., Chen, W., Lin, G., Zhong, R., You, Z., Wang, R., Lu, Y., Wang, R., Huang, Q., Zhang, H., Song, A., Li, C., Wen, Y., Jiang, Y., Liang, H., He, J., Liang, W., ... Liu, J. (2022). Evaluation of clinical and safety outcomes of neoadjuvant immunotherapy combined with chemotherapy for patients with resectable esophageal cancer: A systematic review and meta-analysis. JAMA Network Open, 5(11), e2239778.*

[4] *Wang, Z., Shao, C., Wang, Y., Duan, H., Pan, M., Zhao, J., Wang, J., Ma, Z., Li, X., & Yan, X. (2022). Efficacy and safety of neoadjuvant immunotherapy in surgically resectable esophageal cancer: A systematic review and meta-analysis. International Journal of Surgery, 104, 106767.*

[5] *Huang, F. L., & Yu, S. J. (2018). Esophageal cancer: Risk factors, genetic association, and treatment. Asian Journal of Surgery, 41(3), 210–215.*

[6] *Syllaios, A., Vailas, M., Tolia, M., Charalampakis, N., Vlachos, K., Kapetanakis, E. I., Tomos, P. I., & Schizas, D. (2022). Radiation-induced esophageal cancer: Investigating the pathogenesis, management, and prognosis. Medicina, 58(7), 949.*

[7] *Abnet, C. C., Arnold, M., & Wei, W. Q. (2018). Epidemiology of esophageal squamous cell carcinoma. Gastroenterology, 154(2), 360–373.*

[8] *Li, N., & Sohal, D. (2023). Current state of the art: Immunotherapy in esophageal cancer and gastroesophageal junction cancer. Cancer Immunology, Immunotherapy, 72(12), 3939–3952.*

[9] *Zhao, Y., Li, Y., Zhu, R., Feng, R., Cui, H., Yu, X., Huang, F., Zhang, R., Chen, X., Li, L., Chen, Y., Liu, Y., Wang, J., Du, G., & Liu, Z. (2023). RPS15 interacted with IGF2BP1 to promote esophageal squamous cell carcinoma development via recognizing m6A modification. Signal Transduction and Targeted Therapy, 8(1), 224.*

[10] *Chu, C. Y., Wang, R., & Liu, X. L. (2022). Roles of Wnt/β-catenin signaling pathway related microRNAs in esophageal cancer. World Journal of Clinical Cases, 10(9), 2678–2686.*

[11] *Li, Y., Li, Y., & Chen, X. (2021). NOTCH and esophageal squamous cell carcinoma. Advances in Experimental Medicine and Biology, 1287, 59–68.*

[12] *Zheng, Z., Zhang, B., Yu, H., Li, S., Song, N., Jin, X., & Li, J. (2021). UBE3A activates the NOTCH pathway and promotes esophageal cancer progression by degradation of ZNF185. International Journal of Biological Sciences, 17(12), 3024–3035.*

[13] *Wang, Y., Yang, W., Wang, Q., & Zhou, Y. (2023). Mechanisms of esophageal cancer metastasis and treatment progress. Frontiers in Immunology, 14, 1206504.*