

**A REVIEW ON TIME TREND IN TREATMENT AND SURVIVAL RATE OF
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Article Received on 31/10/2023

Article Revised on 21/11/2023

Article Accepted on 11/12/2023

ABSTRACT

Esophageal cancer and its survival rate remains a challenge even now after progressive advancements in treatment pattern. Even with the introduction of multimodality treatment, the survival rates lies below 30%. The survival becomes increasingly difficult as the stage goes on and it differs among population. This review article will focus on the esophageal cancer treatment patterns and survival rates of different population over 35 years from 1988-2023.

KEYWORDS: EC-Esophageal cancer, ESCC-Esophageal squamous cell carcinoma, EAC- Esophageal adenocarcinoma.

INTRODUCTION

Esophageal cancer stands as one of the most lethal malignancies globally, experiencing a significant surge in incidence in the Western world in recent decades.^[3] Esophageal cancer ranks among the top ten most common cancers worldwide.^[1] The percentage of early esophageal cancer rose from 24.7% in 2005 to 37.2% in 2015.^[2] Esophageal cancer primarily manifests in two histological subtypes: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). On a global scale, ESCC prevails as the predominant type, especially in high-incidence regions of eastern Asia and eastern and southern Africa. In contrast, EAC is the predominant type in Western countries.^[5] Despite the cancer incidence rate being twice as high in developed countries compared to developing ones, a study by Torre et al., as reported by the International Agency for Research on Cancer (IARC), highlights that cancer is acknowledged as the foremost cause of death in developing countries.^[9] Esophageal cancer exhibits a high prevalence among the elderly population, typically manifesting around the age of 65 on average.^[5] In the study conducted by Elaheh Zarean et al., a non-mixture cure fraction model was employed to examine the impact of risk factors on the survival and cure fraction of individuals with esophageal cancer. The findings from their research indicated that females exhibit higher odds of cure compared to males. When evaluating the association between gender and esophageal cancer (EC), numerous confounding variables come into play. Overall, women tend to have a lifestyle less correlated

with smoking habits, tobacco use, alcohol consumption, and other health risk behaviors.^[9] Wu et al. calculated that approximately 48.5% of esophageal cancer cases in China could be attributed to lifestyle-related risk factors. These factors encompassed smoking, high red meat consumption, elevated body mass index (BMI), alcohol consumption, low fruit intake, high processed meat consumption, and insufficient vegetable intake.^[5] Melhado et al. (2010) explored the evolving landscape of esophageal cancer, highlighting a lower risk for women in developing this condition. In a study by Bohanes et al. (2012) that examined gender disparities in survival following an esophageal cancer diagnosis, it was found that men had shorter survival rates, irrespective of whether the cancer was metastatic or loco-regional. The observed discrepancy in survival times between genders was attributed to hormonal differences, particularly with women undergoing menopause. This correlation was further investigated by Mathieu et al. (2012), revealing that higher estrogen levels act as a protective factor against esophageal cancer. Notably, similar patterns were identified in both genders post-menopause among women.^[9]

Diagnosis

The primary pillars in the continuous effort to enhance prognosis are prevention and early detection, with the latter being particularly crucial as it is strongly correlated with tumor stage.^[1] The challenging prognosis and increasing incidence of esophageal cancer underscore the imperative for enhanced detection and prediction

methods that are crucial prior to treatment.^[3] The most significant opportunity for reducing mortality from esophageal cancer lies in its prevention.^[1] Endoscopic screening has the capability to identify precancerous lesions and early-stage cancers in advance, thereby mitigating the risk of cancer through early diagnosis and treatment. This approach contributes to a reduction in the incidence and mortality of esophageal cancer. The study conducted by Ru Chen *et al.* revealed that the age-specific incidence of esophageal cancer peaks after the age of 70. Consequently, there is a necessity to optimize the screening strategy by adjusting the starting and ending ages, aiming to enhance the detection rate while minimizing over-screening.^[5] Delays in the diagnosis and treatment of esophageal cancer lead to poorer survival outcomes. To enhance survival rates and reduce treatment costs, it is essential to implement national screening programs. Additionally, educational initiatives focusing on modifiable risk factors for esophageal cancer, such as cigarette smoking and alcohol consumption, should be rigorously implemented to raise public awareness.^[11]

Treatment

Surgery, chemotherapy, radiotherapy, targeted therapy, and endoscopic treatment constitute the general options for managing esophageal cancer. The selection of a therapeutic approach is primarily determined by the stage of the disease. Currently, the preferred treatment for resectable tumors without metastasis (cT1-3, N0, M0) involves preoperative chemoradiotherapy followed by surgical resection and adjuvant chemotherapy. Notably, primary surgical resection results in microscopic positivity in approximately 25% of cases. As the disease progresses to an advanced stage, resectability diminishes, necessitating the use of neoadjuvant and adjuvant chemoradiotherapy. For patients with stage I disease, surgery alone has shown significantly better overall survival than other treatment modalities, while for those with stage III cancer, surgery alone is associated with significantly worse overall survival. Individuals with clinical stage I disease can undergo esophagectomy without preoperative therapy. Multimodal treatment is recommended for patients with stage II–III esophageal squamous cell carcinoma. Neoadjuvant concurrent chemoradiotherapy before surgery, emerging as the standard protocol for locally advanced operable esophageal cancer, yields better outcomes compared to surgery alone.^[6] Dedicated efforts have been made to optimize surgical treatment, radiotherapy, and chemotherapy, aiming to discover the most efficient combinations of these treatment modalities.^[1] Over the past 30 years, advancements in preoperative diagnostics, surgical techniques, intensive therapy, and adjuvant chemoradiation have empowered specialized centers to achieve remarkable outcomes in operative mortality and 5-year survival rates. This progress has led to the introduction of the term "cure" as one of the attainable goals in the treatment of esophageal cancer.^[4] In the past decades, tumor excision was widely regarded as the most

effective method for treating non-metastatic esophageal tumors. Two distinct trials were conducted to compare surgical and radiotherapeutic monotherapy, and the findings indicate that surgery is more effective, particularly for resectable esophageal tumors. Trimodal chemoradiotherapy combined with surgery is considered the most effective approach in the treatment of esophageal patients who can tolerate the procedure. This method has become the standard approach for patients with grades IB, II, III, and IVA cancer.^[8]

Surgery

Surgery has served as the standard treatment for oesophageal cancer over the past 40 years. During this period, there have been substantial improvements in operative mortality rates as well as one, three, and five-year survival rates. Despite these advancements, the five-year survival rate has remained at a challenging 20%. Notably, a significant survival benefit has been demonstrated for R0 resection (complete removal of the tumor) compared to R1 (tumor reaching resection margins microscopically) and R2 (tumor incompletely removed macroscopically). Traditionally, radiotherapy has been a standard component of oesophageal cancer treatment, either administered alone or in conjunction with surgery.^[1] In locally advanced esophageal cancer, a combination of surgery with other therapies has demonstrated superior survival outcomes compared to definitive concurrent chemoradiotherapy (CCRT). A cohort study conducted by Hye-Kyung Jung *et al.* investigated newly diagnosed esophageal cancer cases at 19 referral hospitals in Korea from January 1, 2005, to December 31, 2017. For patients with stage Ia disease, those treated with endoscopic resection (31.9%) exhibited a median survival time similar to those undergoing surgery (9.9 years vs. 10.5 years, log-rank test $p = 0.82$). Among patients with stage Ib disease, esophagectomy was associated with significantly longer overall survival (OS) compared to CCRT (9.8 years vs. 4.8 years, $p < 0.001$). For patients with stage II–III disease, surgery with combined therapy demonstrated significantly longer OS compared to definitive CCRT (6.9 years vs. 1.5 years, $p < 0.001$). Notably, esophagectomy with multi-modality therapy was performed in 79.8% of patients with stage II-III, showing improved OS compared to other countries. Surgery with multi-modality therapy is increasingly favored for patients with locally advanced esophageal cancer (more than 50% of patients), providing better survival comparable to that of definitive CCRT.^[2] A database comprising 4627 patients revealed a 3-year survival rate of 30 percent for individuals with stage III squamous cell carcinoma (SCC) treated with oesophagectomy.^[10] Over the years, the percentage of patients undergoing surgery has seen an improvement, increasing from 55% in the 1970s to 64% between 2000 and 2007.^[4] Notably, postoperative complications stand out as a major contributor to mortality associated with esophageal cancers.^[11] In a study by Amsalu Degu *et al.*, esophagectomy emerged as the sole significant

determinant of survival for early-stage patients (stage I and II). This underscores the critical role of surgical intervention in influencing survival outcomes, particularly in the early stages of esophageal cancer.^[11]

Chemotherapy

Chemotherapy in oesophageal cancer is pursued with two primary objectives: (i) reducing the recurrence of occult lymphatic metastases to potentially improve survival, and (ii) achieving tumor shrinkage to increase resectability rates. It is not recommended as the sole adjuvant treatment outside of clinical studies or trials. The primary goal is to identify drug combinations with higher response rates than the currently used combinations of 5-FU and cisplatin. There is a broad consensus on the benefits of multimodality therapy for oesophageal cancer. Most current trials involve combinations of chemotherapy, radiotherapy, and surgery. The focus is either on surgery with various adjuvant chemotherapy, radiotherapy, or combined chemoradiotherapy schemes, or on chemoradiation with additional surgical resection for nonresponders. The emphasis on combining multiple modalities reflects a comprehensive approach to address the complexities of oesophageal cancer treatment.^[11] For patients with stage II–III disease, significantly longer overall survival (OS) was observed in association with both neo-adjuvant therapy (3.5 years) and adjuvant therapy (3.8 years). This suggests a positive impact on survival outcomes for individuals undergoing either neo-adjuvant or adjuvant therapy in the context of stage II–III disease.^[12] In the study conducted by Seyed Kazem Mirinezhad *et al.*, the chemotherapy regimen consisted of 5-fluorouracil (5-FU) plus cisplatin. The specific dosages were 5-FU administered at 1000mg/m² on days 1–4, given every 3 weeks in two courses, and cisplatin administered at 100mg/m² on day 1.^[7]

Survival

The survival of esophageal cancer is predominantly influenced by several key factors, including age, the stage of cancer at presentation, and the type of treatment.^[7] Factors such as aggressive tumor biology, an advanced disease stage at the time of presentation, and a poor response to treatment collectively contribute to a diminished prognosis and poorer survival outcomes.^[10]

Survival figures in esophageal cancer exhibit significant variation across different treatment protocols, a variability partly attributed to differing pre-treatment conditions. The attainment of a pathological complete response to chemoradiotherapy has been identified as a significant factor in enhancing survival. Despite advancements in surgical technique and perioperative mortality over the past decade, there have been only slight improvements in five-year survival rates. In response to this, a multimodal therapy approach and extended lymphadenectomy were introduced with the aim of achieving higher cure rates and reducing recurrence from occult metastases. However, the impact

of therapy on overall survival in esophageal cancer has shown only marginal improvement over the last two decades, with five-year survival rates ranging from 10%–15% before 1988 to approximately 15%–20% in recent studies. Notably, the prognosis is significantly better for early tumor stages, with over 70% five-year survival for stage I and II tumors, compared to a 0% five-year survival in stage IV tumors.^[11] In a study by Hye-Kyung Jung *et al.* conducted between January 2005 and December 2017, a total of 6,354 patients treated at 19 Korean centers were identified. The distribution of treatment modalities was as follows: surgery alone (31.3%), definitive concurrent chemoradiotherapy (CCRT) (27.0%), neoadjuvant therapy (12.4%), adjuvant therapy (11.1%), and endoscopic resection (5.8%). The 5-year overall survival rate was 45.7 ± 0.7%. Endoscopic resection demonstrated a similar median survival to surgery for stage Ia cases. Among stage II–III cases, definitive CCRT was associated with poorer survival compared to neoadjuvant or adjuvant therapy, with no significant survival difference between neoadjuvant and adjuvant therapy. Early esophageal cancer is gradually becoming more common, and endoscopic resection provides similar long-term survival relative to surgery. The overall survival intervals were 9.6 years for stage I disease, 4.3 years for stage II, 1.8 years for stage III, and 0.9 years for stage IV. However, there was no significant difference among patients with stage IIb or stage IIc disease when comparing definitive CCRT and surgery with combined therapy. Endoscopic resection was associated with a low rate of serious complications and a comparable long-term survival rate. The 5-year overall survival rates were 77.9% for stage Ia disease and 71.0% for stage Ib disease. The 5-year survival rate in patients with stage II–III disease was 39.4%, with better survival observed for neoadjuvant or adjuvant therapy compared to definitive CCRT. Endoscopic resection provided similar long-term survival compared to surgery in early cancer.^[12] In the study conducted by Seyed Kazem Mirinezhad *et al.*, the mean age of participants was 65.8 ± 12.2, with an age range spanning from 29 to 90 years at the time of diagnosis. The survival rates at 1, 3, and 5 years after diagnosis were reported as 55%, 18%, and 12%, respectively. Kaplan-Meier analysis revealed that the survival rates at 1, 2, 3, 4, and 5 years after diagnosis were 55%, 26%, 18%, 13%, and 12%, respectively.^[7] According to the Surveillance, Epidemiology, and End Results (SEER) database, which included 64,433 patients, the reported 5-year overall survival rate among individuals with localized esophageal cancer was 29%. This information was reported by B.-Y. Wang *et al.*^[10] In a study conducted by Elaheh Zarean *et al.* on 127 patients during 2009–2010 in East-Azarbaijan, Iran, the one, three, and five-year survival probabilities were reported as 0.44, 0.2, and 0.13, respectively. The patients were followed up for 5 years. In comparison, the 5-year survival rate for people with esophageal cancer (EC) in the United States has been reported as 18% (Siegel *et al.*, 2016). The reported survival time ranged from 0.10 to 69.03 months in the study conducted in Iran.^[9] In a study

by Attila Dubecz *et al.*, the ten-year survival for all patients was reported as 14%. The cure rate demonstrated improvement across all stages during the study period. Specifically, after the year 2000, the cure rates were 73%, 37%, 12%, and 2% for stages 0, 1, 2, and 4, respectively. Additionally, the proportion of patients diagnosed with in situ and local cancer remained below 30%. These findings highlight both the overall survival rates and stage-specific variations in esophageal cancer outcomes.^[4] Despite advancements in the management and treatment of esophageal cancer patients, the overall outcome remains notably poor, with 5-year survival rates ranging from 10% and 5-year post-esophagectomy survival rates falling within the range of 15-40%. The challenges arise from the frequent diagnosis of esophageal cancer in advanced stages, primarily due to the absence of early clinical symptoms. To enhance patient outcomes after surgery, neoadjuvant concurrent chemoradiotherapy (CCRT) is often employed to reduce tumor size. Multimodality neoadjuvant CCRT has gained popularity in esophageal cancer treatment, with randomized trials demonstrating a significant survival rate benefit when neoadjuvant CCRT is followed by surgery for patients with locally advanced esophageal cancer. Postoperative adjuvant therapy has shown positive effects, improving disease-free survival rates and reducing the length of hospital stays for nonresponder patients with esophageal squamous cell carcinoma (ESCC). In nonsurgical local ESCC patients, chemotherapy efficacy was evaluated using nimotuzumab (200 mg) weekly, paclitaxel (175 mg/m²) on Day 1, and cisplatin (30 mg/m²) on Days 1 and 2, with the cycle repeating every 3 weeks over six cycles, resulting in an overall response rate of 51.8%. For patients with esophageal adenocarcinoma, neoadjuvant chemoradiotherapy has been widely employed to treat those with locally advanced and/or lymph node-positive tumors. In a study involving 205 patients with T2-T4 or lymph node-positive esophageal adenocarcinoma, neoadjuvant chemoradiotherapy followed by surgery resulted in a 19% pathologic complete response rate. The 3-year overall survival and recurrence-free survival rates for these patients were 86% and 80%, respectively, indicating the specificity of neoadjuvant chemoradiation therapy to esophageal adenocarcinoma.^[3] According to evidence gathered by Seyed Mokhtari *et al.*, 15 to 30 percent of patients treated with neoadjuvant chemotherapy exhibit complete pathological remission, where the tumor is entirely treated and no longer exists. These patients demonstrate a 3-year survival rate of 50%. Early systemic chemotherapy, combined with local radiotherapy and surgical procedures, aids in limiting the spread of cancer, consequently increasing survival rates. In a cohort of 168 patients who underwent neoadjuvant chemoradiotherapy, 150 (89.2%) were alive, while 18 (10.8%) had passed away. Comparatively, among 112 patients who did not receive neoadjuvant chemoradiotherapy, 79 (70.5%) were alive, and 33 (29.5%) were deceased. The average survival rate for the neoadjuvant chemoradiotherapy group was 27.20 ± 5.21 ,

whereas the untreated group had an average survival rate of 7.12 ± 5.86 . In the study, the first-year postoperative survival rate for the treated subjects was 97.61% (n=164). Among the untreated subjects, 88 (78.571%) were alive after the first year checkpoint. Another study conducted by Stahl *et al.* revealed that the 3-year survival rate after preoperative radiotherapy increased from 27.7% to 47.4%. When comparing third-year survival rates, a 21% rise was observed in the survival rates of patients who underwent preoperative chemoradiotherapy. Similarly, a study by Ancona *et al.* concluded that patients with resectable esophageal cancer who received preoperative chemoradiotherapy achieved complete remission and higher long-term survival rates compared to opposing groups. In a study by Walsh *et al.*, it was determined that preoperative chemotherapy followed by resection resulted in less esophageal tissue resection but higher rates of complete resection (RO) compared to surgical-only treatments.^[8] A previous systematic review in Africa indicated a slightly improved survival with esophagectomy and chemoradiation therapy. However, the 5-year overall survival rate remains minimal, with low cure possibilities. Despite the availability of various treatment options such as surgery, chemotherapy, radiation therapy, and targeted therapy, achieving the desired treatment goal remains challenging, and the prognosis remains poor. In the study by Amsalu Degu *et al.*, the 1 and 5-year survival rates were reported as 86% and 25%, respectively, and the survival rate decreased from 2 to 5 years. Most participants in the study had an advanced stage of the disease, likely linked to late-onset symptoms, which significantly impact desired treatment outcomes. The 5-year survival rate of 25% among study participants was lower than the mean survival time observed in western countries, which was longer than that of Ethiopian esophageal cancer patients (10 months vs. 4 months). Additionally, the overall 3-year survival rate in the Ethiopian study (2.4%) was lower compared to the setting in western countries (56%). These disparities suggest that cancer care may not be adequate in African countries. Long-term overall survival was observed in locally advanced esophageal cancer patients treated with chemoradiation and surgery. Radiotherapy, chemotherapy, chemoradiation, and comorbidity were identified as significant determinants of survival in advanced-stage patients.^[11] The overall survival rate in a study conducted by Jilcha Diribi Feyisa *et al.* was very low, with 6 months, 1-, and 2-year survival rates of 54.6%, 19.5%, and 2.0%, respectively. A pathological complete response of 29% was achieved in patients who underwent resection after chemoradiotherapy. In another study, the median overall survival was 49.4 months for patients treated with neoadjuvant chemoradiotherapy followed by surgery, compared to 24.0 months for patients treated with surgery alone. The long-term survival of patients with esophageal cancer, particularly for localized disease, has improved over the past few decades in various regions. In a Taiwanese study group, the 3-year overall survival rates were 60.65% for patients with stage I disease, 36.21% for those with stage II

cancer, and 21.39% for patients with stage III carcinoma. In China, the five-year survival rate of patients with Esophageal Squamous Cell Carcinoma (ESCC) increased from 3.6% to 21.1% between 1973 and 2010. However, a study in the United States on the survival of esophageal cancer patients revealed a 10-year survival rate of 14%. In Ethiopia, the survival of patients with esophageal cancer has not shown significant improvement over the decades, highlighting the challenges and disparities in cancer care in different regions.^[6]

CONCLUSION

Survival rate and early diagnosis have a correlation. Treatment in the early stage has a better survival rate so diagnosis in the early stage is crucial. Progressive advancements are achieved in treatment, Despite the fact that overall survival still remains below 30%.

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