ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCE

SCHOOL OF MEDICINE

Treatment Outcome of FOLFOX versus Carboplatin–Paclitaxel as First line Therapy for Advanced Squamous Cell Carcinoma of the Esophagus at TASH, Addis Ababa Ethiopia: A comparative Retrospective Study.

By: Ikram Musa (MD)

Thesis to be submitted to the school of medicine, college of health sciences, Addis Ababa university in partial fulfillment of the requirements for the speciality certificate in clinical oncology.

DECEMBER, 2025.

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Full title

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ADVISOR'S APPROVAL SHEET

This is to certify that the thesis entitled "Treatment Outcome of FOLFOX versus Carboplatin–Paclitaxel as First-Line Therapy for Advanced Squamous Cell Carcinoma of the Esophagus at TASH, Addis Ababa Ethiopia: A comparative Retrospective Study", submitted in partial fulfillment of the requirements for the Specialization Certificate in Clinical Oncology to the Department of Clinical Oncology, College of Health Sciences, Addis Ababa University, has been carried out by Dr. Ikram Musa under my supervision. Therefore, I recommend that the student has fulfilled the requirements and hereby submit the thesis to the Department.

Dr. Mathewos Assefa (Consultant Oncologist) _____ _____

Dr Sonia Worku (Consultant Oncologist) _____ _____

Name of Major Advisor Signature Date

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Catalog

TITLE

Abbreviations

ESCC Esophageal squamous cell carcinoma

EAC Esophageal adenocarcinoma

CT Chemotherapy

5FU 5 fluorouracil

FOLFOX 5Flourouracil+oxaloplatin+leucovorine

CTCAE Common Terminology Criteria for Adverse Event

ORR Overall response rate

OS Overall survival

PFS- progression free survival

RECIST Response Evaluation Criteria in Solid Tumor

TASH Tikur Anbessa Specialized Hospital

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Abstract

Background: Esophageal squamous cell carcinoma (ESCC) is one of the most common sub-types of esophageal cancer in Sub-Saharan Africa. The majority of patients present with unresectable or metastatic disease usually accompanied with malnourishment and poor general condition. FOLFOX and Carboplatin/Paclitaxel are used as first-line therapy for advanced diseases. However, there is no data on the comparative effectiveness and safety of these regimens Africa.

Objective: To Compare the Treatment Outcome of FOLFOX versus Carboplatin–Paclitaxel as First-Line Therapy for Advanced Squamous Cell Carcinoma of the Esophagus.

Methods: Patients with stage IV esophageal squamous cell carcinoma treated between February 2023- February 2025 who met the inclusion and exclusion criteria who were included .Data was analyzed using descriptive statistics, Kaplan-Meier curves, log-rank tests, and multivariable analysis to compare outcomes between treatment groups.

Results: A total of 55 patients with stage IV esophageal squamous cell carcinoma were included, with a median age of 56 years. Thirty patients (54.5%) received carboplatin–paclitaxel and 25 (45.5%) received FOLFOX.The overall response rate was higher with carboplatin–paclitaxel than FOLFOX at both mid-cycle (67.9% vs. 47.8%) and end-cycle assessments, with greater mean tumor reduction (66.3% vs. 49.4%, p = 0.038).The median overall survival (OS) for the entire cohort was 9 months (95% CI: 7.2–10.3), with a 1-year OS of 45%. Median OS was 9.0 months for carboplatin–paclitaxel and 8.0 months for FOLFOX, with no significant difference between regimens (p = 0.286). Treatment-related toxicities occurred in 52.7% of patients, predominantly hematologic. Grade 3–4 neutropenia was observed in 10.9%. Severe hematologic toxicities were more common with carboplatin–paclitaxel (16.7% vs. 4.0%), whereas peripheral neuropathy occurred more frequently with FOLFOX (8.0% vs. 0%).

Key words-Esophageal Squamous cell carcinoma, response rate, treatment related toxicity, FOLFOX, Carboplatin-paclitaxel, Survival

1-INTRODUCTION

1.1 Background

Esophageal cancer is the most common cancer worldwide.it ranks as the eleventh most frequent malignancy and the seventh leading cause of cancer related death world(1).From pathologic stand point it is primarily divided as esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma(EAC) which have distinct epidemiological characteristics, genetic profiles and outcomes(2,3).Although ESCC represented the most common sub-type of esophageal cancer, in regions like Northern America, Northern Europe and Oceania number (and proportion) of EAC cases exceeded those of ESCC(4). The burden of ESCC is especially pronounced in the so-called "esophageal cancer belt," a region stretching from northern Iran through Central Asia to north-central China. In these areas, nearly 90% of esophageal cancer cases are squamous cell carcinoma. Sub-Saharan Africa is another high-incidence region, with more than 22,000 cases reported in 2018 alone (4,)

More than half of patients are unsuitable candidate for definitive surgery at the time of diagnosis (5,6) .This is mainly due to late presentation with loco regional unresectable or metastatic disease and most of the time it is coupled with malnourishment and poor general condition. Data from National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registry indicates that 22% of ESCC patients are diagnosed with stage III disease and 27% of patients have stage IV disease. The 5-year relative survival of ESCC is 15.9%(7).

In Ethiopia 80% of esophageal cancer patients are diagnosed in later stages of the disease.(8,9) Effective treatment options are limited and unmet highlighted by the reported poor prognosis with of a median survival of 4–8 months(8). For most patients with locoregional advanced disease or with distant metastasis the primary focus of treatment is effective palliative care aimed at improving g quality of life and prolonging survival.

The commonly used regimens as front line systemic chemotherapy in advanced ESCC are FOLFOX and the carboplatin–paclitaxel combination. Despite their routine use at Tikur Anbessa Specialized Hospital, there is no data directly comparing their effectiveness and toxicity. Therefore, it is fundamental to understand the available systemic treatment options and outcomes for Ethiopian patients with advanced ESCC.

1.2-Statement of the Problem

In Ethiopia, esophageal squamous cell carcinoma (ESCC) often presents at an advanced or metastatic stage when curative approaches such as surgery or chemoradiotherapy are no longer viable options (9). Consequently, systemic chemotherapy remains the primary treatment

option for patients with advanced disease, aiming to palliate symptoms, delay disease progression, and prolong survival.

The management of advanced ESCC remains a major challenge. Study on the real-world outcomes in patients with first-line and second-line therapy for advanced esophageal squamous cell carcinoma reported that patients receive short duration of therapy(1.4month),and overall survival (16-18months) continues to be poor(10). Fluoropyrimidine (5-fluorouracil [5-FU] or capecitabine) combined with cisplatin(11) continue to be the preferred first line treatment options worldwide. Studies proposed that the use of oxaliplatin in combination of 5-FU, a less toxic regimen,may be another treatment option for ESCC. Findings from one study reported that FOLFOX6 regimen has shown moderate anti-tumor activity as first line treatment with a well-tolerated toxicity profile in metastatic ESCC. (12)

A recent systematic review on the treatment of east Asian patients with advanced ESCC summarized that both platinum plus taxane and platinum plus fluoropyrimidine regimens are effective as first line treatment, and cab be used in this setup. However , the prognosis for patients receiving these treatments remains poor (13). Hematological toxicities were common with both regimens. Head-to-head comparative data are required to confirm the relative efficacy and safety of the two regimens (13).

Recent development, A notable progress in ESCC management, use of immunotherapy in combination with chemotherapy has resulted in an extension of overall survival by approximately 18 months(10),however the availability of immunotherapy in resource limited countries like Ethiopia remains restricted due to substantial cost. Although systemic chemotherapy is the standard treatment in the unresectable, metastatic or recurrent ESCC, the availability of effective and well tolerated palliative chemotherapy options is limited. Therefore, it is important to understand the available therapeutic options and associated outcomes for Ethiopian patients with advanced ESCC.

The absence of such context-specific evidence presents a critical gap in clinical decision-making. It leaves oncologists without clear guidance on which regimen may offer better clinical response rate, survival outcomes and fewer adverse effects in our setting where patients may have poor nutritional status, limited access to advanced treatment options and reduced access to consistent follow-up and supportive care. By evaluating response rates, overall survival and toxicity, the study aims to generate critical local evidence that can help standardize care, inform clinical guidelines and ultimately improve outcomes for this patient population.

1.3-Significance of the Study

This retrospective study aims to address pivotal lack in knowledge by comparatively evaluating the response rate and adverse effect of FOLFOX versus Carboplatin/Paclitaxel as first-line therapy for advanced ESCC. The findings hold significant value for several ways.by comparing response rates (ORR) and overall survival (OS) between the two regimens, this study will provide valuable data to guide clinicians in selecting the most effective first-line treatment for individual patients with advanced ESCC.in addition to that evaluating f treatment-related adverse events will help clinicians understand the safety profile of each regimen allowing for a more balanced risk-benefit assessment when choosing the best treatment approach for each patient.

Overall, this study has the potential to improve treatment decisions for patients with advanced ESCC by providing data on the comparative effectiveness, and safety of FOLFOX and Carboplatin/Paclitaxel regimens. This knowledge can ultimately contribute to improved patient outcomes and quality of life.

CHAPTER 2: LITERATURE REVIEW

2.1 Epidemiology of Esophageal cancer: Global Burden and Trends

Esophageal cancer is a highly aggressive malignant disease. Approximately 604,100 cases globally were recorded in 2020 up from 450,000 cases in 2012. Notably, it ranks as the seventh most common cancer worldwide(1).Unfortunately, progress in the treatment of esophageal cancer has been limited in the last two decades and it remains the sixth leading cause of cancer-related deaths globally. In 2020, esophageal cancer led to 544,000 deaths which reflects an increase from 400,000 cases in 2012(1,3).

Esophageal cancer has two main histology subtypes: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). In Asia and Africa, ESCC continues to be the most common form of this cancer, while in Europe and the United States EAC is most common. In the area with the highest incidence of esophageal cancer ,referred as the esophageal cancer belt, spanning from northern Iran across Central Asia to the north-central regions of China approximately 90% of individuals diagnosed with esophageal cancer present with ESCC (7,14).

Ethiopia lies at the epicenter of the East African ESCC corridor and reports some of the continent's highest burdens of ESCC. More than 80% of EC cases in the country are squamous cell carcinoma. At the time of presentation, approximately 50–60% of patients are unsuitable candidates for surgery. Most of the patients are diagnosed at an advanced stage, and the prognosis of patients with metastatic esophageal cancer is extremely poor(8,14).

For most patients with advanced esophageal cancer, the primary goal of treatment is effective palliative care aimed at improving quality of life and extending survival. In addition to this , ESCC was associated with poorer survival compared with EAC (6).

2.2 Treatment Patterns of Advanced Esophageal Cancer

2.2.1 Global Perspective on Systemic Therapy

Systemic chemotherapy plays an essential role in the treatment of patients aiming to palliate symptoms and prolong survival(7,13).Cisplatin and 5-fluorouracil (5-FU) (CF) based chemotherapy demonstrated partial efficacy for esophageal cancer and is recognized as the standard chemotherapy for advanced esophageal cancer(13).

In attempts to improve outcomes of this devastating disease, numerous clinical trials have been conducted to investigate other effective and less toxic therapeutic agents. Including carboplatin with paclitaxel, Oxaliplatin-based combination regimens like FOLFOX, CAPOX, Combination cisplatin with 5FU and Single agent chemotherapy like docetaxel (12,13,15–17).

2.2.2 Treatment Patterns in Ethiopia

In Ethiopia, treatment of advanced ESCC is centered at Tikur Anbessa Specialized Hospital (TASH) and a few regional oncology units. Commonly used regimens include Cisplatin + 5-FU (CF), Paclitaxel + Cisplatin (TP), FOLFOX (5-FU + oxaliplatin) when available, Paclitaxel monotherapy in frail patients. Evidence on regimen effectiveness is scarce. Studies have reported modest improvements in survival among patients receiving chemotherapy compared with supportive care alone, but toxicity remains a major barrier to treatment completion in ESCC and EAC(9,12,18).

2.3. Toxicity Profiles and Response rate

2.3.1 FOLFOX

The overall response rate with FOLFOX regimen was 23.2% with a disease control rate of 67.9%.(10,12). Toxicities observed with FOLFOX were generally moderate and reversible. The most common hematologic toxicity was neutropenia. six (10.7 %) patients experienced grade 4 neutropenia , four (7.1 %) patients experienced leukopenia . Four (7.1%) patients had febrile neutropenia. However, the duration was brief and no infection occurred. Grade 3 anemia was reported in six (10.7%) patients. Thrombocytopenia occurred in six (10.7%) patients. The most frequent non-hematologic toxicity was mucositis, nausea/vomiting, fatigue and peripheral neuropathy. Neuropathy was generally mild to moderate. Grade 2 peripheral neuropathy was observed in only three (5.4 %) patients, which was reversible did not require a dose reduction or discontinuation of oxaliplatin(12).

2.3.2carboplatin/paclitaxel

Several paclitaxel-based combination regimens were tested in clinical trials. Carboplatin plus paclitaxel demonstrated a considerable antitumor activity in a retrospective study and an early phase trial with a response rate of 39–43% (19,20).Cisplatin plus paclitaxel was tested in a Phase 2 trial, resulting in an encouraging efficacy with a response rate of 48.6% (21). Paclitaxel plus 5-FU plus cisplatin also showed a considerable efficacy with a response rate of 48% in a Phase 2 trial for patients with advanced esophageal cancer, including about 50% of patient with ESCC, but a high incidence of toxicities required hospitalization of 48% of patients(16)The most common toxicities were neutropenia and alopecia. No grade 4 toxicities and treatment-related deaths were recorded in all patients(21).

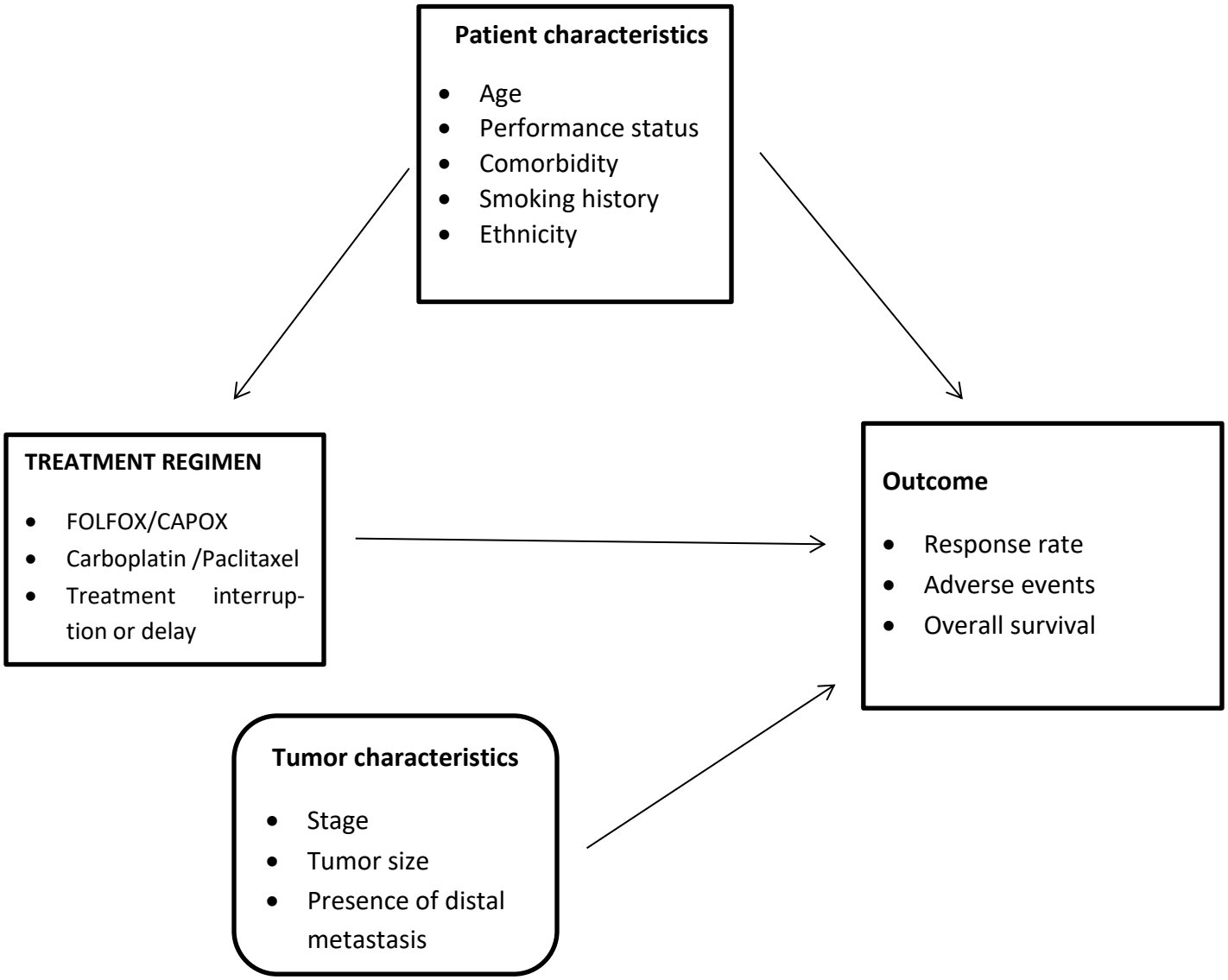
Although triplate chemotherapy with paclitaxel–cisplatin–5FU has better tumor control in ESCC higher toxicity was noted with grade 3 neurologic toxicity occurred in 18 % of patients, grade 3/4 fatigue in 35 %, stomatitis in 24 %, diarrhea in 14 %, neutropenia in 57.4 % and thrombocytopenia in 14.8 % of patients. Approximately half of the patients enrolled required a dose reduction due toxicity; 48% of the patients required hospitalization due to febrile neutropenia(16).

2.4 Survival of Esophageal Cancer in Adult Patients

The median PFS of 4.4 months and a median survival time of 7.7 months had been demonstrated with the use of FOLFOX6 regimen as first-line treatment for ESCC in Japanese study(12).For carboplatin /paclitaxel the median survival time of 9 months and the 1-year survival rate was 43% has been documented for carboplatin/Paclitaxel(20).Mortality is exceptionally high in the sub-Saharan region due to late presentation, limited diagnostic facilities, and restricted access to oncology services. Mortality-to-incidence ratios exceed 95% in many African countries, compared with 89% globally(14) .This underscores the urgent need for improved early detection, treatment access and region-specific clinical research.

Median survival after diagnosis is extremely poor in Ethiopia. A major retrospective cohort study from Tikur Anbessa Specialized Hospital (TASH) reported a median survival of only four months, with 3-year survival at just 2.4%(9).Most patients are malnourished, anemic, and have poor performance status at presentation—factors that significantly influence tolerance to chemotherapy. The overall survival rate was very low with 6 months, 1-, and 2-year survival rates of 54.6% (95%CI:47.5%-61.2%), 19.5% (13.8% -25.9%), and 2.0% (0.45%–5.9%), respectively. Inconclusion survival outcome remans poor, several clinical factors including performance status,satge and treatment delay has been consistently associated with prognosis(9).

Although different kinds of available chemotherapy have been studied to improve efficacy and reduce toxicity in the first-line treatment of unresectable and metastatic ESCC the poor performance status of patients with advanced ESCC might hinder the prescription of any therapy with a high toxic profile. At present, there is no consensus on the optimal palliative first-line chemotherapy regimen for patients with advanced esophageal squamous cell carcinoma (ESCC) TASH, Ethiopia .In this regard, our study Is conducted to investigate the efficacy and toxicity of carboplatin/paclitaxel vs. FOLFOX treatment to afford enough clinical evidence for first-line chemotherapy in patients with unresectable and metastatic ESCC.



Conceptual frame work indicating possible relationship between Dependent and independent variables

3-Objectives

3.1-General Objective:

1-Compare the treatment outcome of FOLFOX and Carboplatin/Paclitaxel as first-line therapy for patients with advanced Squamous Cell Esophageal Cancer.

3.2-Specific Objectives:

1. To determine the objective response rate (ORR) in both treatment arms.
2. To evaluate the incidence of grade 3 adverse effects of the treatment.
3. To compare overall survival (OS) between patients receiving FOLFOX and Carboplatin/ Paclitaxel regimens.

4-Methods and Procedures

4.1-Study Area and Study period: This study was conducted at Addis Ababa University Oncology department from September 2025 to December 2025.Addis Ababa is the capital city of Ethiopia. Tikur Anbessa Hospital is one of Ethiopia's leading tertiary care centers, serving as a national referral hospital for complex cases and providing specialized care to patients from across the country, with a population of over 120 million. The Hospital provides health services for approximately 25 thousand inpatients and 400 thousand outpatients a year with a bed capacity of 732. At present, the majority of esophageal cancer cases are diagnosed and treated within surgery and adult Oncology units.

4.2-Study design:

- This study employed a retrospective Study design.

4.3-Source Population:

- The source population consisted of all charts of patients with Stage 4A or Stage 4B esophageal squamous cell carcinoma treated between February 2023 to February 2025 at TASH.

4.4-Study Population:

- Adults (age 18 years or older) patients with Stage 4A or Stage 4B esophageal squamous cell carcinoma (SCCE) based on AJCC Version 8 staging criteria between 2023 and 2025 who fulfill the inclusion criteria was included in the study.

4.5- Inclusion Criteria:

- Histologically confirmed diagnosis of Stage 4A or Stage 4B esophageal squamous cell carcinoma (SCCE).
- Chemotherapy -naive (no prior chemotherapy for esophageal cancer).
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
- Adequate liver, and kidney function
- No prior history of malignancy (except for adequately treated basal cell or cervical carcinoma in situ).

4.6-Exclusion Criteria:

- Patients with adenocarcinoma or other histological subtypes.
- Incomplete or missing treatment/outcome data
- Patients who didn't take their course of chemotherapy at TASH

4.7-Variables

4.7.1Dependent Variable:

- Objective Response Rate (ORR)
- Treatment-related adverse effects
- overall Survival (OS)

4.7.2-Independent Variable:

- Treatment Regimen
  - ✓ FOLFOX
  - ✓ Carboplatin/paclitaxel
- Treatment delay
- Age
- Performance Status
- Comorbidities
- Tumor Stage
- Smocking
- Ethnicity

4.8-Sample size calculation

Sample Size

A census of all patients who met the inclusion criteria during the two-year study period February 2023 to February 2025 were included.

4.9-Data Collection:

- Data was collected by last year residents from patient medical records at TASH Oncology Center, Ethiopia, The EMRs of eligible patients were reviewed.

Baseline data including

- Demographic information (age, gender, ethnicity)
- Medical history (comorbidities, prior surgeries)
- Tumor characteristics (stage, size, location) based on imaging
- Performance status (ECOG score)
- Laboratory test results (blood counts, liver function tests, kidney function tests)
- Baseline dysphagia grade

Treatment details –including regimen received (FOLFOX or Carboplatin / Paclitaxel), dosage, number of cycles, any treatment delays or modifications during treatment ware reviewed

Response to therapy: Tumor response was recorded according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) in patients with measurable lesions.

Patient-reported outcomes and Treatment-related side effects information was gathered by reviewing patient record (EMRs), and phone calls to evaluate treatment outcomes.

4.10-Data Analysis

Statistical analysis was performed using a software package such as SPSS version 29.Descriptive statistics were used to summarize baseline characteristics. The response rates were calculated as proportions with corresponding confidence intervals. Kaplan- Meier curves were used to estimate OS. Log-rank tests were used to compare between the two groups. The incidence of specific AEs between treatment groups was compared using Fisher- exact test.All tests were two-sided, value of $P<0.05$ is accepted as statistically significant.

Reporting: All statistical results were presented with their corresponding p values and confidence intervals. Tables and figures were used to effectively present the findings.

4.11-Operational definition

1- Esophageal cancer:

- Definition: - Malignant tumor that arise from the esophagus
- Measurement: Diagnosed based on histopathological examination and classified based on histology.

2-Patient Demographics:

- Definition: Characteristics of the patient population, including age, sex, ethnicity
- Measurement: Collected from patient records at the time of diagnosis and during treatment.

3 Clinical Characteristics:

- Definition: Medical conditions and features of the disease in patients, such as tumor stage, Location, and presence of comorbidities.
- Measurement: Extracted from patient medical records and diagnostic reports.

4-Performance Status:

- Definition: Performance status refers to a patient's general well-being and ability to carry out daily activities. It is an important prognostic factor in cancer treatment and can influence treatment decisions and outcomes.
- Measurement: Performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale, which is a standardized measure.

5-Stage of esophageal Cancer:

- Definition: The stage of esophageal cancer refers to the extent of the disease based on the depth of invasion of the tumor, the involvement of lymph nodes, and the presence of metastasis. Staging is crucial for treatment planning and prognosis.
- Measurement: The stage of esophageal cancer was determined using AJCC staging (8^{th} edition)

6 Palliative Treatments

- Treatment aimed at alleviating symptoms, improving quality of life, and possibly prolonging survival without intending to cure the disease.

7. Treatment Response

a) Responder

Patients who show a measurable reduction in tumor burden following treatment.

• Complete Response (CR): Disappearance of all target lesions for at least 4 weeks, with no new lesions detected.

• Partial Response (PR): A ≥30% reduction in the sum of the diameters of the target lesions compared to baseline, sustained for at least 4 weeks.

b) Non-Responder

Patients who show little or no reduction in tumor burden or disease progression despite treatment.

• Stable Disease (SD): Tumor size does not meet the criteria for PR or progressive disease (PD). Changes in tumor size are minimal and fall between a 20% increase and a 30% reduction.

• Progressive Disease (PD): A ≥20% increase in the sum of the diameters of the target lesions or the appearance of new lesions.

• No Response Assessment: Patients who did not undergo post-treatment evaluation to determine response, regardless of treatment received.

8-OS

- Definition: The duration of time from the date of start of treatment to the date of death from any cause or the last date of follow-up if the patient is still alive.
- Measurement: Recorded in months, using patient follow-up records, from the initial Treatment date to either the date of death or the end of the study period on November 30, 2025.

9-Adverse Events; define as any treatment-related undesired effects that developed during treatment

10-Treatment Outcome-Response rate, overall survival, adverse effects

11 -Advanced Esophageal Squamous cell carcinoma- unresectable, metastatic, and recurrent disease.

4.9. Ethical statement

Ethical clearance and approval for the study was obtained from Institutional Ethics Review Board of Health Institute, Addis Ababa University. Permission was obtained from AAU administration and privacy will be maintained.

4.10. Dissemination plan and use of the result

The findings of this study will be presented to the department of Clinical Oncology for thesis defense. Summary report will be submitted to AAU and result will also be communicated to clinicians who treat the patient to identify factors that could be focused on to improve outcome in this setting. Effort will be made to publish the findings in peer reviewed journals.

5-Result

Socio-demographic and disease characteristics

Between February 1, 2023, and February 1, 2025, the medical records of 55 patients with stage IV squamous cell carcinoma of the esophagus that met the inclusion and exclusion criteria were treated at Tikur Anbessa Specialized Hospital (TASH) were retrospectively reviewed.

In this cohort, 65.5% of patients were female. With respect to residence, 34% were from Oromia and 29% from Addis Ababa. Most patients had good performance status; with 90% classified as ECOG 1 and 10% was ECOG 2. The mean tumour size (longest diameter measured by CT or endoscopy) was 12.4 (SD ± 3.4 cm) (table 1).

Table 1: Baseline sociodemographic and disease characteristics of advanced ESCC patients at oncology unit of TASH, Addis Ababa Ethiopia, 2023 to 2025.

Patient characteristics (N=61)	Frequency (n)	Percent %
Age range in years		
Less than and equal to 60	37	67.3
Greater than 60	18	32.7
Alcohol consumption		
Yes	7	12.7
No	47	85.5
Unknown	1	1.8
Smoking cigarettes		
Yes	12	21.8
No	43	78.2
Comorbidity		
No-comorbidity	36	65.5
HIV	3	5.5
HTN (Hypertension)	7	12.7
DM (Diabetes Mellitus)	5	9.1
HTN plus DM	4	7.3
Main symptom at presentation		
Dysphagia	55	100
Weight loss	21	38.2

Regurgitation	14	25.5
Heartburn	12	21.8
Vomiting:	5	9.1
Other symptoms 3 patients (5.5%)	3	5.5
Dysphagia grade at presentation		
Grade I	15	27.3
Grade II	19	34.5
Grade III	15	27.3
Grade IV	6	10.9
Location of tumor		
Cervical	1	1.8
Upper thoracic	18	32.7
middle thoracic	22	40.0
Lower thoracic	14	25.5
Stages		
Metastatic	8	14.54
Non-metastatic	47	85.45
Site of metastasis		
Lung	6	75.5
Live	1	12.5
multi-site	1	12.5

Treatment characteristic

Chemotherapy regimen

Among the 55 participants, 54.5% received carboplatin–paclitaxel, while 45.5% were treated with FOLFOX. The specific dose regimens administered were either carboplatin (AUC 5) plus paclitaxel (175 mg/m²) in 33 patients (60.0%), or FOLFOX comprising 5-fluorouracil (400 mg/m² bolus then 600 mg/m² infusion) with oxaliplatin (85 mg/m²) in 22 patients (40.0%). Most carboplatin-paclitaxel patients (84.8%) received treatment every 3 weeks, while nearly all FOLFOX patients (95.5%) were treated every 2 weeks, reflecting their respective standard administration schedules.

Treatment completion status and dose modification

The number of chemotherapy cycles administered ranged from 2 to 6. The majority of patients (63.6%) received 6 cycles and 20.0% received 3 cycles. The proportion completing 6 cycles was similar between FOLFOX (60.0%) and carboplatin-paclitaxel (66.7%) group. Treatment modification (dose reduction, or regimen change) occurred infrequently in this cohort. Only 8.0% of FOLFOX and 6.7% of carboplatin-paclitaxel patients were required dose modification (p=1.000, Fisher's exact test).

Treatment delay during chemotherapy

Treatment delays were common, occurring in half of the cohort (50.9%). The remaining 49.1% received their chemotherapy on schedule without delays. Among patients who experienced delays, hematologic toxicity was the predominant reason, accounting for 81.5% of delays. Specifically, neutropenia (ANC <1000/µL) caused 59.2% of delays, while concurrent anaemia and neutropenia accounted for 22.2%. Non-hematologic causes included electrolyte imbalance (7.4%), thrombocytopenia (3.7%), and poor performance status (ECOG 3-4, 3.7%). Among the 28 patients who experienced treatment delays, the median delay was 8-14 days (39.3%) followed by 7 days in 25.0%, and 10.7% experienced delays of 22-30 days.

Treatment delays occurred with similar frequency in both treatment arms. 48.0% of FOLFOX patients experienced delays, compared to 53.3% of carboplatin-paclitaxel patients. This difference was not statistically significant (p = 0.789, Fisher's exact test). Delay durations showed regimen-specific trends, FOLFOX had longer delays (>3 weeks: 25% vs. 0%), while carboplatin-paclitaxel had more moderate delays (2-3 weeks: 31% vs. 8%). These differences, while not statistically significant (p=0.164), may suggest different toxicity recovery patterns.

Chemotherapy response assessment

Mid-cycle response assessment and factors predicting response

Mid-cycle response assessments were done for 92.7% of patients. Response evaluations were performed by using chest CT scan in all patients who had mid-cycle evaluation. Among the 51 patients who had mid-cycle evaluation, the partial response rate was 58.8% with an additional 23.5% achieving stable disease and 17.7% had progressive disease. Among the 9 patients who experienced progressive disease at mid-cycle assessment, the site of progression was predominantly locoregional (55.6%).

Distant progression occurred in 33.3%, and 11.1% progressed at both locoregional and distant sites. The tumor response differed substantially between treatment arms. Carboplatin-paclitaxel demonstrated superior anti-tumor activity, with 67.9% of patients achieving a partial response compared to 47.8% with FOLFOX. Correspondingly, treatment failure with progressive

disease was more than twice as frequent in the FOLFOX arm (26.1% vs. 10.7%), though these differences did not reach statistical significance in this sample (p=0.293 by Fisher's exact test)

Logistic regression analysis of mid-cycle tumour response did not identify any statistically significant predictors of non-response (stable disease plus progressive disease). The choice of chemotherapy regimen showed a non-significant trend, with FOLFOX associated with higher odds of non-response compared to carboplatin-paclitaxel in both univariable (OR=2.1, p=0.1) and multivariable analyses (aOR=2.3, p=0.10). Similarly, the occurrence of any chemotherapy delay prior to mid-cycle was associated with an elevated but non-significant odd of non-response in the univariable model (OR=2.6, p=0.10), an association lost magnitude in the multivariable model (aOR=1.8, p=0.50). Analysis by delay duration (<7 days vs. ≥7 days) also showed no significant association (multivariable aOR=0.6, p=0.5) (table 2).

Table 2: Factors associated with treatment response outcomes at mid-cycle: Univariable and multivariable binary regression analyses

Variable characteristics		Univariable regression		Multivariate regression	
variable	category	ORR (ref.) vs non-responder.		ORR (ref.) vs non-responder.	
		OR	p-value	aOR	P-value
Treatment type	Carboplatin/paclitaxel	Ref		Ref	
	FOLFOX	2.1 (0.-7.5)	0.10	2.3 (0.7-7.7)	0.10
Delay in any cycle of chemotherapy	Any delay	2.6(0.8-8.2)	0.10	1.8(0.3-10.3)	0.50
	No delay	Ref	-	-	
Duration of delay during chemotherapy cycle	<7day delay	0.4 (0.1-1.3)	0.10	0.6(0.1-3.6)	0.5
	>7-day delay	Ref	-	Ref	

End-cycle response assessment and factors predicting response

End-cycle response assessments were done for 78.2% of patients. Response evaluations were performed by using chest CT imaging in all patients who had end-cycle evaluation. At end-cycle

evaluation complete response rate was 11.6% and partial responses were 62.8%. Only 7.0% of evaluable patients had progressive disease at treatment completion. Among these, progression involved both local and distant sites in 2 patients (66.7%) and was locoregional only in 1 patient (33.3%). No patients had distant-only progression at treatment completion. At the end-cycle evaluation, patients experienced a mean tumour size reduction of 56.1%, with a median reduction of 66.3%, indicating that most patients achieved substantial tumour shrinkage. Among the three patients with progressive disease and evaluable data, the mean percentage change indicated a tumour increase of 28.7%, with a median increase of 30% compared with baseline .

Patients treated with carboplatin/paclitaxel achieved a greater mean reduction compared with those receiving FOLFOX (approximately 66.3% vs 49.4%, respectively). This corresponds to a mean difference in tumour reduction of 16.9 percentage points, which was statistically significant on Welch's t-test ($t = 2.16$, $p = 0.0380$. Carboplatin-paclitaxel was associated with a high complete responses rate compared to FOLFOX (16.0% vs. 0%), though the overall distribution of response categories did not differ significantly between arms ($p=0.347$ by Fisher's exact test). Progressive disease was also less frequent with carboplatin-paclitaxel compared to FOLFOX (4.0% vs. 11.8%).

Our logistic regression analysis evaluated the association between treatment regimen, chemotherapy delays, and the odds of non-response (stable or progressive disease) at the end of treatment showed that neither the choice of initial chemotherapy regimen (FOLFOX vs. carboplatin-paclitaxel) nor the occurrence of treatment delays were statistically significant independent predictors of short-term tumour non-response. The FOLFOX regimen was associated with non-significant higher odds of non-response (aOR = 1.7, p = 0.40). However, there is a strong trend toward any chemotherapy cycle delay substantially increased the odds of non-response (aOR = 5.0, p = 0.12) (table 3).

Table 3: Factors associated with treatment response outcomes at end-cycle: Univariable and multivariable binary logistic analyses

Variable characteristics		Univariable regression		Multivariate regression	
Variable	Category	ORR (ref.) vs non-Responder		ORR (ref.) vs non-Responder	
		OR	p-value	aOR	P-value
Treatment type	Carboplatin	Ref.	-	Ref	
	FOLFOX	1.3 (0.3 – 5.5)	0.6	1.7 (0.3 – 7.1)	0.4
Delay in any cycle of chemotherapy	Any delay	3.8 (0.8 – 17.0)	0.07	5.0 (0.7 – 35.3)	0.12
	No delay	Ref	-	-	
Duration of delay during chemotherapy cycle	<7day delay	0.5 (0.1 – 2.2)	0.30	0.6 (0.08 – 4.6)	0.60
	>7 day delay	Ref	-	Ref	

Toxicity profile in each arm

Among the 55 evaluated patients, treatment-related grade 3 toxicities were observed in 40% of patients. The most frequent adverse events were hematologic. Neutropenia was the predominant toxicity, occurring in 30.9% of patients, with grade 3-4 neutropenia (<500 cells/µL) observed in 10.9%. Other hematologic toxicities included anaemia with neutropenia (7.3%) and thrombocytopenia (1.8%, n=1). Non-hematologic toxicities were less common, with peripheral neuropathy and electrolyte imbalance each reported in 3.6% of patients. None of the patients experienced renal toxicity (Table 4).

Comparison of toxicity profiles between treatment arms revealed clinically distinct patterns, though the overall distribution did not differ statistically (Fisher- exact test, p=0.176. The carboplatin-paclitaxel arm demonstrated higher rates of severe hematologic toxicities occurring in 16.7% versus 4.0% in the FOLFOX arm. In contrast, peripheral neuropathy was 8.0% in FOFOX vs zero percent in carboplatin/ paclitaxel.

Table 4- Overall toxicity profile observed in the study cohort (n=55)

Toxicity		Frequency (N)	Percent (%)
No toxicity		26	47.3
Hematologic toxicities	Neutropenia (500-1000 cells/µL)	11	20.0
	Neutropenia (<500 cells/µL)	6	10.9
	Anaemia plus neutropenia	4	7.3
	Thrombocytopenia(<50,000cells/µL)	1	1.8
Non-Hematologic toxicities	Peripheral neuropathy	2	3.6
	Electrolyte imbalance	2	3.6
Mixed hematologic plus non-hematologic		2	3.6

Survival outcome

At the end of study 80% of patient had died and 20% was alive. Overall survival was assessed using the Kaplan–Meier method. The median overall survival was 9 months (95% CI: 7.2-10.3). The 1-year overall survival rate was 45% (Figure 1). The median overall survival (OS) was 8.0 months (95% CI, 6.6 to 9.4) for the FOLFOX group and 9.0 months (95% CI, 6.3 to 11.7) for the carboplatin-paclitaxel group. A log-rank test comparing the survival distributions showed no statistically significant difference between the two treatment arms (Log-Rank test, p = 0.286). The occurrence of any chemotherapy cycle delay was significantly associated with reduced overall survival. Patients experiencing a delay had a median survival of 7.0 months (95% CI: 5.3

to 8.7), compared to 11.0 months (95% CI: 6.3 to 15.7) for patients with no delays (log-rank test, p = 0.003) (figure 2). A delay of 7 days or more for any chemotherapy cycle was associated with significantly worse overall survival. The median survival was 6.0 months (95% CI: 3.1 to 8.9) for patients with a ≥7-day delay, compared to 9.0 months (95% CI: 6.2 to 11.8) for patients with delays of less than 7 days (log-rank test, p = 0.008) *(figure 3)*.

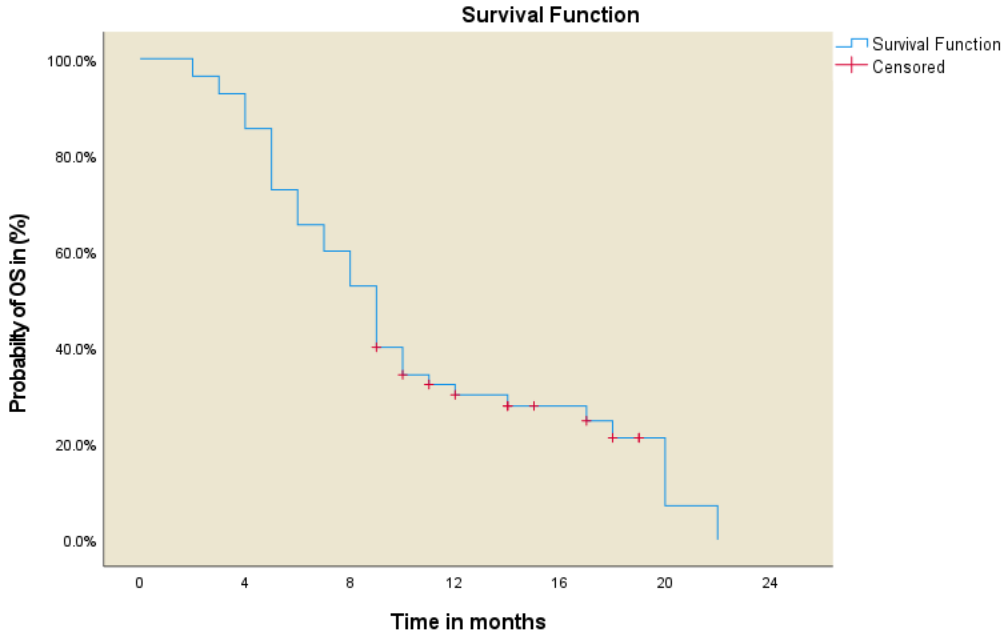


Figure 1: Kaplan–Meier curve showing overall survival of the study cohort

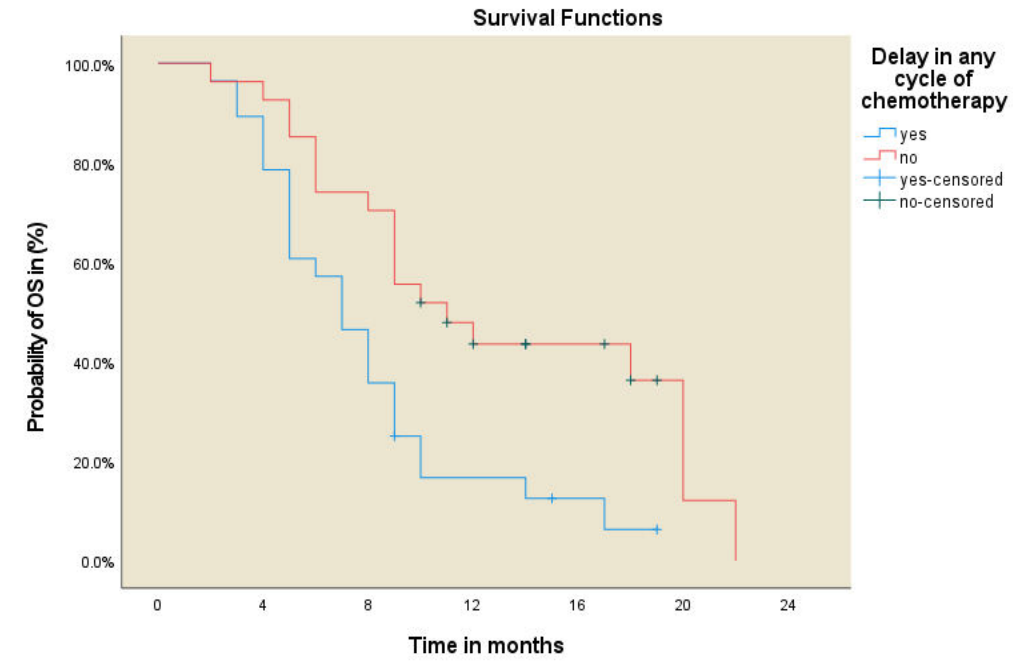


Figure 2: Kaplan-Meier curve for overall survival by chemotherapy delay status

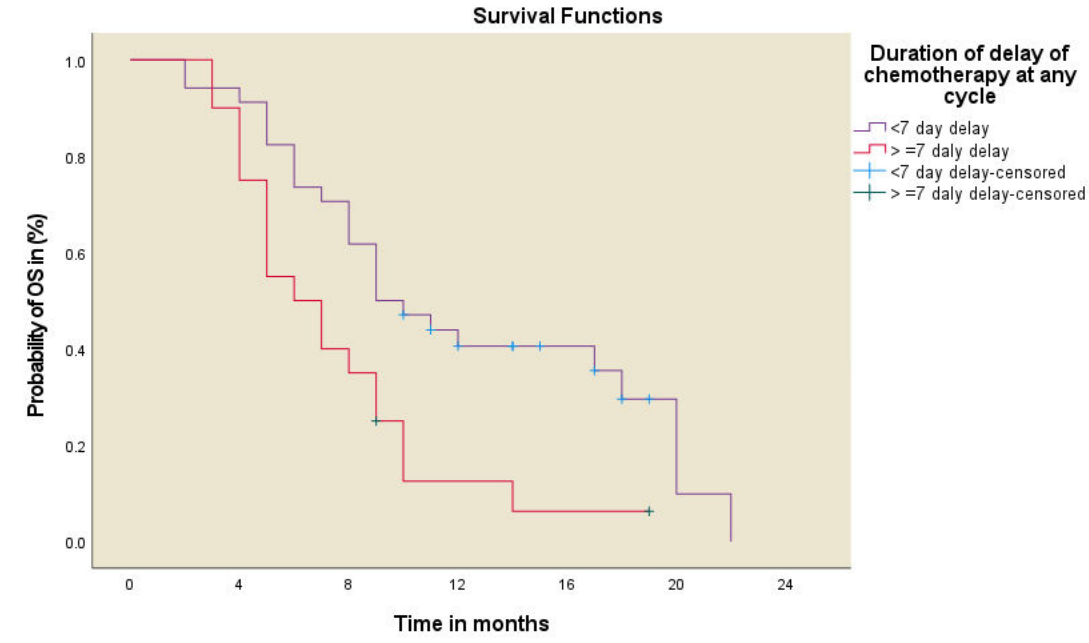


Figure3: Kaplan-Meier curve for overall survival by duration of chemotherapy delay

Prognostic factors for overall survival

In this analysis, treatment schedule adherence emerged as a significant prognostic factor, while the choice of initial chemotherapy regimen did not. Univariable Cox regression showed that avoiding any chemotherapy cycle delay was associated with a 60% lower risk of death compared to experiencing a delay (HR = 0.4, 95% CI: 0.2-0.7, p=0.006). Similarly, a delay shorter than seven days was associated with a 55% lower risk compared to a delay of seven days or more (HR = 0.45, 95% CI: 0.24-0.86, p=0.01). In contrast, the difference between carboplatin-paclitaxel and FOLFOX was not significant (HR = 0.7, 95% CI: 0.4-1.3, p=0.20). In the multivariable model, adjusting for other factors, the association for 'no delay' attenuated and was no longer statistically significant (HR = 0.4, 95% CI: 0.2-1.1, p=0.08) (table 5).

Table 5. Univariable and multivariable Cox regression analysis for overall

Variable characteristics			Univariable		Multivariable	
Variable	Category	Patient numbers (N)	HR (95% CI)	P-value	HR (95%CI)	P-value
Treatment type	FOLFOX	25	ref.			
	Carbo/Paclitaxel	30	0.7 (0.4-1.3)	0.20	0.6 (0.3-1.23	0.22
Delay in any cycle of chemotherapy	Any delay	27	ref.			
	No delay	28	0.4 (0.7)	0.006	0.4 (0.2-1.1)??	0.08
Duration of delay of chemotherapy at any cycle	<7 day	34	Ref		ref.	
	≥7 day	20	2.2(1.4-4.2)	0.01	1.2(0.5-3-0)	0.6

6-DISCUSSION

This retrospective study evaluated tumor response, toxicity, and survival among patients with stage IV esophageal squamous cell carcinoma (ESCC) treated with carboplatin–paclitaxel or FOLFOX at Tikur Anbessa Specialized Hospital (TASH). To our knowledge, this is among the few studies from Ethiopia directly comparing these two commonly used regimens in a real-world clinical setting.

The majority of patients in this study (65.5%) were female which is not consistent with many global studies, which report ESCC to be more prevalent in males. Nonetheless, some regions of East Africa reported similar patterns, indicating regional variations of risk factors and distribution of the disease (3,8)The majority of patients had a good baseline performance status (ECOG 1–2), indicative of management of care selection practices, and patients with poor functional status are less likely to receive systemic chemotherapy in this setting .A mean tumor size of 12.4 cm highlights the advanced disease burden in this cohort and is consistent with prior Ethiopian studies indicating that initial diagnosis of ESCC is often delayed as most patients are coming from rular area ,due to access to care and inadequate recognition of symptoms(8,9). They are also contributing factors to the poor prognosis in advanced ESCC patients.

There was relatively balanced use of both regimens suggests clinical equipoise, with treatment decisions influenced more by drug availability that is reasonable to the patient, the kind of patient who tolerates treatment and the clinicians' preference than by hard data on the superiority of one vs the other (12,18,20).

Two thirds of the patients completed six chemotherapy cycles (approximately 66%) with similar overall completion rates across regimens. But those who received FOLFOX were most likely to stop their treatment at three cycles. This may be a consequence of accumulation toxicity or practical difficulties of the bi-weekly administration approach, challenging to maintain within resource limited setting (15,18). Treatment delay was observed in more than half of the sample and hematologic toxicity was the major factor. This result corroborates previous study finding myelosuppression as a significant restriction of chemotherapeutic response in ESCC (11,12,16).

Although the overall frequency of delays did not differ significantly between regimens, distinct patterns were observed, with FOLFOX associated with longer delays. Such disparities may be due to the toxicity recovery characteristics which vary with the regimen. Crucially, treatment delay was identified as a highly important clinical factor affecting survival of patients. Patients who had a delay had significantly shorter median overall survival compared with those who received chemotherapy on schedule. Furthermore, delays of seven days or more were associat-

ed with particularly poor survival. These findings underscore the importance of maintaining chemotherapy dose intensity and schedule adherence in patients with advanced ESCC.

When we see response to chemotherapy regimens, Mid-cycle response assessment demonstrated a partial response rate of 58.8%, with carboplatin–paclitaxel showing a numerically higher response rate than FOLFOX. Although this difference did not reach statistical significance. Progressive disease occurred more frequently in the FOLFOX arm, consistent with findings from some phase II trials of oxaliplatin-based regimens (10,12).At end-cycle evaluation, both regimens achieved substantial tumor reduction. Notably, carboplatin/paclitaxel was associated with higher complete response rates.

In our study more than half of the patients experienced treatment-related toxicity, with hematologic adverse events being the most common. Neutropenia was the predominant toxicity, consistent with previous reports for both regimens (16,18,22). Severe hematologic toxicity was more frequent in the carboplatin–paclitaxel arm, whereas peripheral neuropathy occurred more commonly in patients receiving FOLFOX, reflecting the known neurotoxicity associated with oxaliplatin.

Our study revealed that the median overall survival of nine months observed in this study is comparable to outcomes reported in other studies of advanced ESCC treated with systemic chemotherapy (10,22). No statistically significant survival difference was observed between treatment regimens, supporting existing evidence that no single cytotoxic regimen offers clear survival superiority in metastatic ESCC (6,13). No significant difference in survival between treatment paradigms was observed, corroborating evidence that any one cytotoxic regimen does not confer clear survival advantage in metastatic ESCC (6,13). The delay in treatment was the highest prognostic factor of survival although the relationship decreased in multivariable analyses.

Clinical implications and future directions

In the Ethiopian context, where patients often present with advanced disease and limited supportive resources, treatment strategies should prioritize tolerability, cost, ease of administration and the ability to maintain treatment schedules. Both carboplatin–paclitaxel and FOLFOX appear to be reasonable first-line options, however based on higher tumor response rate and every three-week administration of carboplatin /paclitaxel can be preferred over FOLFOX. However, interventions aimed at reducing treatment delays—such as proactive toxicity management and improved supportive care—may have a greater impact on survival than regimen selection alone.

Strengths and limitations

The strengths of this study include its real-world design and comprehensive assessment of response, toxicity, and survival at Ethiopia's largest oncology center. Limitations include the retrospective nature of the study may introduce biases due to significant incomplete medical records, which may not provide a full picture of the toxicity profile and outcomes of esophageal cancer patients, small sample size, and lack of quality-of-life data, which limit generalizability and causal inference.

Conclusion

In conclusion, survival outcomes for patients with advanced ESCC treated at TASH remain poor and comparable to international reports. No significant survival difference was observed between carboplatin–paclitaxel and FOLFOX. Treatment delays emerged as the most clinically relevant factor influencing survival, highlighting the importance of treatment adherence and supportive care. Carboplatin/paclitaxel seems a reasonable option for most patients because of easy of administration. Prospective studies are needed to define optimal, context-appropriate treatment strategies for ESCC in Ethiopia.

Recommendations

1. Clinical Practice

1. Both FOLFOX and carboplatin–paclitaxel may be used as first-line chemotherapy for patients with advanced esophageal squamous cell carcinoma, as no significant difference in overall survival was observed.
2. Given the higher tumor response rate and three-weekly administration schedule, carboplatin–paclitaxel may be preferred in settings where maintaining treatment adherence is challenging.
3. Prevention and early management of chemotherapy-related toxicities, particularly hematologic toxicities, should be strengthened to reduce treatment delays.
4. Efforts should be made to minimize chemotherapy delays, as treatment interruption was the most important prognostic factor affecting survival.

2. Institutional and Research

1. Strengthening supportive care services and standardizing treatment follow-up may improve chemotherapy adherence and outcomes.

2. Prospective studies with larger sample sizes are recommended to further evaluate optimal first-line treatment strategies for advanced esophageal squamous cell carcinoma in Ethiopia.

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ANNEXS

Annex-1

Standard Data Collection Tool

This outlines the standard data collection for the retrospective study comparing FOLFOX and Carboplatin/Paclitaxel for advanced squamous cell esophageal cancer.

A. Demographics and Baseline Characteristics

1. Age_____

2. Gender

3. Ethnicity_____

4. Co-morbidity

5. Smoking history

    1. Yes

    2. No

    3. Unknown

6. Alcohol consumption history

    1. Yes
    2. No
    3. Unknown

7. Performance status_____

B . Tumor Characteristics

8. Tumor location

9. Tumor stage

10. Tumor size (based on imaging)_____

11. Non metastatic(TNM)_____

12. Presence of distant metastasis

A. Liver B. Lung C. Pleural space D. Spine E. Bone other than spineF. Lymphnodes

I. Celiac II.Retroperitoneal III. Supra-clavicular

G. Other metastatic site (specify)_____

D. Treatment Data

15. Treatment arm

1. FOLFOX
2. Carboplatin/Paclitaxel
3. Cisplatin/Paclitaxel

16. Chemotherapy start date(dd/mm/yr)_____

17. Specific details of each regimen

I.Dosing,(per m2) _____

II.Schedule, _____

III. Total cycle_____

18. Any treatment modifications or delays

1. Yes
2. No
3. Unknown

19. If yes for Drug modification

I. Type of Drug modified_____

II. Percentage of the modified drug reduced_____

III. At which cycle the drug modified_____

IV. Cause of drug modification_____

B. If yes for Delay of cycle of chemotherapy

I.At which cycle_____

II. Duration of delay_____

III. Cause of delay_____

E. Response to Therapy

20. Mid-cycle assessment

I. Dates of imaging assessments _____
II. Type of imaging assessments _____
III. Mid Cycle Grade of dysphagia_____

21. Tumor response according to RECIST criteria (mid-cycle)

I. Complete response,
II. Partial response,
III. Stable disease,
IV. Progressive disease

22. Progressive disease,Site of progression(at mid-cycle assessment),

I. Distant(specify site)_____
II. Loco-regional
III. Both

23. Percentage change in tumor size_____

24. End-cycle assessment

I.Dates of imaging assessments _____

II. Type of imaging assessments _____

III. End Cycle Grade dysphagia_____

25. Tumor response according to RECIST criteria (End-cycle)

I. Complete response,
II. Partial response,
III. Stable disease,
IV. Progressive disease

26. Progressive disease,Site of progression(end cycle assessment)

I. Distance(specify)_____
II. Loco-regional
III. Both

27. Percentage change in tumor size_____

F. OS

28. Patient alive

A. Yes B. No

Annex-2

CTCAEs.V5

Anemia,Thrombocytopenis,Neutropenia

Blood and lymphatic system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability. **Navigational Note:** -					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen. **Navigational Note:** -					
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen. **Navigational Note:** -					
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow. **Navigational Note:** -					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen. **Navigational Note:** -					
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.					

Renal Toxicity: **Serum Creatinine**

CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Definition: A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen. **Navigational Note:** Also consider Renal and urinary disorders: Acute kidney injury				

Annex 3

Dysphagia Grading scale

Grade 0: Able to eat solid food without special attention to bite size or chewing

Grade 1: Able to swallow solid food cut into pieces less than 18 mm in diameter and thoroughly chewed

Grade 2: Able to swallow semisolid food (consistency of baby food)

Grade 3: Able to swallow liquids only

Grade 4: Unable to swallow liquids or saliva

Performance status

Performance status	Definition
0	Fully active; no performance restrictions
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work
2	Capable of all selfcare but unable to carry out any work activities. Up and about >50 percent of waking hours.
3	Capable of only limited selfcare; confined to bed or chair >50 percent of waking hours
4	Completely disabled; cannot carry out any selfcare; totally confined to bed or chair