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TO DETERMINE THE FREQUENCY OF COMPLETE PATHOLOGICAL RESPONSE IN RESECTABLE ESOPHAGEAL SQUAMOUS CELL CARCINOMA PATIENTS TREATED WITH INDUCTION CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMORADIATION AND SURGERY

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ABSTRACT

Background: Esophageal squamous cell carcinoma is an aggressive malignancy associated with poor prognosis and high mortality.

Objective: To determine the frequency of pathological complete response in patients with resectable esophageal squamous cell carcinoma treated with induction chemotherapy followed by concurrent chemoradiotherapy and surgery.

Methods: This prospective observational study was conducted at the Department of Clinical and Radiation Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Peshawar, from June 2025 to November 2025. A total of 116 patients aged 30–70 years with histologically confirmed resectable esophageal squamous cell carcinoma (T1–T3, N0–N1, M0) were included through non-probability convenience sampling. Baseline demographic, clinical, and tumor-related characteristics were recorded. Patients underwent induction chemotherapy followed by concurrent chemoradiotherapy and definitive surgery.

Results: The mean age was 54.8 ± 9.6 years, with male predominance (68.1%). Most patients presented with T3 disease (56.0%) and nodal involvement (62.1%). Pathological complete response was achieved in 38 (32.8%) patients, while R0 resection was achieved in 101 (87.1%). Patients achieving pathological complete response were significantly younger (51.2 ± 8.7 vs. 56.5 ± 9.8 years; p=0.006) and more likely to have ECOG 0–1 status (78.9% vs. 55.1%; p=0.01), earlier tumor stage (p<0.001), N0 disease (p=0.003), and favorable histological differentiation (p=0.01).

Treatment-related toxicity occurred in 52.6% of patients, most commonly fatigue (36.2%), nausea/vomiting (29.3%), and esophagitis (25.0%).
Conclusion: Induction chemotherapy followed by concurrent chemoradiotherapy and surgery demonstrated favorable pathological response and high surgical clearance rates in resectable esophageal squamous cell carcinoma, with acceptable tolerability, supporting its role as an effective multimodal treatment strategy.
KEYWORDS: Esophageal squamous cell carcinoma; pathological complete response; induction chemotherapy

INTRODUCTION

Esophageal cancer is one of the most aggressive gastrointestinal tracts malignancies, and is an important public health problem because of its incidence and mortality [1]. It is linked to poor prognosis as it is usually diagnosed at late stages when there are limited treatments for cure [3]. Of the histological types, esophageal squamous cell carcinoma (ESCC) is still the most common type in developing countries, especially in South Asia where tobacco consumption, nutritional deficiency, low socioeconomic status, and environmental exposures are major factors in the occurrence of this cancer [2]. The burden of ESCC in Pakistan remains significant and often the disease is diagnosed at a locally advanced yet potentially resectable stage. Surgical resection has long been the mainstay treatment for resectable esophageal carcinoma. But surgery has proven to have poor long-term results, with five-year survival not exceeding 50% and the risk of recurrence still being high [4]. Despite proper preoperative staging and technically successful resections, microscopic residual disease and occult metastases frequently contribute to disease failure [6]. With these restrictions came a growing interest in multimodal approaches to treatment, with a focus on enhancing survival and reducing recurrence. Neoadjuvant chemotherapy was added to shrink the tumor, to make it easier to be removed by surgery and to treat micrometastatic disease before definitive surgery [5]. This approach did have some success in improving outcomes, but the survival benefits were not consistent, and combinations of treatments were explored to improve the treatment. Later, the combination of chemotherapy and radiation therapy (concurrent chemoradiotherapy) became more effective as a neoadjuvant treatment because the two therapies work together to have a greater effect than either working alone. Chemotherapy increases the radiosensitivity of tumors by impairing the ability of tumor cells to repair after radiation, by making all tumor cells radiotherapeutically sensitive by pushing them into a sensitive phase of the cycle and by improving the oxygenation of tumors, while radiotherapy provides better control of the tumor in the local area. The paradigm shift of neoadjuvant concurrent chemoradiotherapy (CRT) and surgery for resectable esophageal cancer. This combination has been shown to provide superior rates of resection (R0) [9] together with superior pathological response and significantly improved survival compared to surgery alone in the landmark CROSS trial. This treatment strategy has been shown to have long-term survival benefits and is now considered a standard treatment for locally advanced resectable esophageal cancers [10]. Pathological complete response (pCR), defined as the absence of viable malignant cells in the resected surgical specimen after neoadjuvant treatment, has become an important prognostic indicator that is correlated with better disease free and overall survival outcomes [12]. More recently, induction chemotherapy prior to concurrent chemoradiotherapy has been investigated to further decrease tumour load and to eliminate occult systemic disease at an earlier stage of disease (induction therapy) [14].

Objective

To determine the frequency of pathological complete response in patients with resectable esophageal squamous cell carcinoma treated with induction chemotherapy followed by concurrent chemoradiotherapy and surgery.

METHODOLOGY

This was a prospective observational study conducted at the Department of Clinical and Radiation Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Peshawar, from June 2025 to November 2025, including 116 patients. Male and female patients aged 30–70 years with histologically confirmed resectable esophageal squamous cell carcinoma (T1–T3, N0–N1, M0) involving the mid or distal esophagus, with or without gastroesophageal junction involvement, who were planned for induction chemotherapy followed by concurrent chemoradiotherapy and surgery, were included. Patients willing to provide informed consent were considered eligible. Patients with unresectable esophageal carcinoma, metastatic disease, recurrent esophageal squamous cell carcinoma, age greater than 70 years, histological subtypes other than squamous cell carcinoma including adenocarcinoma or neuroendocrine carcinoma, and patients unwilling to participate were excluded.

Data Collection

After obtaining ethical approval and informed written consent, eligible patients were enrolled through the outpatient department using non-probability convenience sampling. Baseline demographic and clinical information were recorded using a structured proforma, including age, gender, disease duration, tumor stage, performance status,

nutritional status, and relevant clinical history. Patients selected through multidisciplinary team recommendations underwent induction chemotherapy followed by concurrent chemoradiotherapy according to institutional treatment protocols. Patients were prospectively followed throughout treatment to monitor tolerability and treatment-related toxicities. Following completion of therapy, all patients underwent surgical resection, and postoperative histopathological examination was reviewed to determine pathological complete response, defined as absence of viable malignant cells in the resected specimen with R0 resection margins.

Statistical Analysis

Data were analyzed using SPSS version 20. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Stratification was performed for variables including tumor stage, performance status, treatment-related toxicities, and resection margin status. Chi-square test was used for comparison between stratified groups. A p-value ≤0.05 was considered statistically significant.

RESULTS

The mean age of patients was 54.8 ± 9.6 years, with most patients aged 50–59 years (47, 40.5%). Males were predominant (79, 68.1%) compared with females (37, 31.9%). The mean symptom duration was 5.7 ± 2.4 months. Most patients had good ECOG performance status 0–1 (73, 62.9%), while mild malnutrition was present in 49 (42.2%) patients.

Table 1: Baseline Demographic and Clinical Characteristics of Patients with Resectable Esophageal Squamous Cell Carcinoma (N = 116)

Variable	n (%) / Mean ± SD
Age (years)	54.8 ± 9.6
30–49 years	38 (32.8)
50–59 years	47 (40.5)
≥60 years	31 (26.7)
Gender	
Male	79 (68.1)
Female	37 (31.9)
Duration of symptoms (months)	5.7 ± 2.4
ECOG Performance Status	
0–1	73 (62.9)
2	35 (30.2)
3	8 (6.9)
Nutritional status	
Normal	42 (36.2)
Mild malnutrition	49 (42.2)
Moderate/severe malnutrition	25 (21.6)

Most tumors were located in the mid esophagus (68, 58.6%), followed by distal esophagus (39, 33.6%). T3 disease was most common (65, 56.0%), and nodal involvement was present in 72 (62.1%) patients. Moderately differentiated tumors were the most frequent histological grade (67, 57.8%).

Table 2: Tumor Characteristics and Staging Profile of Study Population (N = 116)

Variable	n (%)
Tumor location	
Mid esophagus	68 (58.6)
Distal esophagus	39 (33.6)
Gastroesophageal junction involvement	9 (7.8)
Tumor stage (T stage)	
T1	12 (10.3)
T2	39 (33.6)
T3	65 (56.0)
Nodal status	
N0	44 (37.9)
N1	72 (62.1)
Histological grade	

Well differentiated	19 (16.4)
Moderately differentiated	67 (57.8)
Poorly differentiated	30 (25.9)

Patients received a mean of 2.4 ± 0.6 induction chemotherapy cycles. Planned induction chemotherapy was completed by 104 (89.7%) patients, while 98 (84.5%) completed concurrent chemoradiotherapy. R0 resection was achieved in 101 (87.1%) patients. Pathological complete response was observed in 38 (32.8%), while residual viable tumor remained in 78 (67.2%) patients.

Table 3: Treatment Characteristics and Response Outcomes (N = 116)

Variable	n (%) / Mean ± SD
Number of induction chemotherapy cycles	2.4 ± 0.6
Completed planned induction chemotherapy	104 (89.7)
Completed concurrent chemoradiotherapy	98 (84.5)
Underwent definitive surgery	116 (100)
R0 resection achieved	101 (87.1)
Pathological complete response (pCR)	38 (32.8)
Residual viable tumor present	78 (67.2)

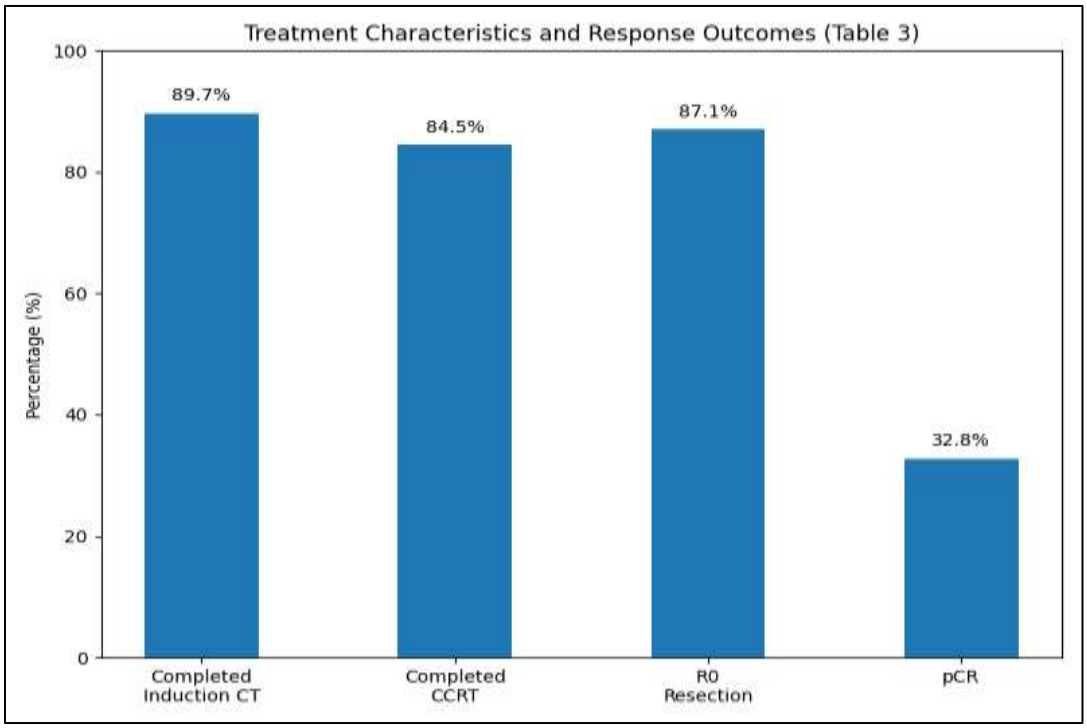

Figure 1: Treatment Characteristics and Pathological Response Outcomes in Patients with Resectable Esophageal Squamous Cell Carcinoma

Patients achieving pCR were younger than those without pCR (51.2 ± 8.7 vs. 56.5 ± 9.8 years; p=0.006). pCR was significantly associated with better ECOG status 0–1 (30, 78.9% vs. 43, 55.1%; p=0.01), earlier T1–T2 stage (26, 68.4% vs. 25, 32.1%; p<0.001), N0 disease (22, 57.9% vs. 22, 28.2%; p=0.003), and well/moderately differentiated histology (34, 89.5% vs. 52, 66.7%; p=0.01). Gender showed no significant association with pCR (p=0.42).

Table 4: Association of Pathological Complete Response with Clinical Variables

Variable	pCR Achieved (n=38)	No pCR (n=78)	p-value
Age (years), mean ± SD	51.2 ± 8.7	56.5 ± 9.8	0.006
Male gender, n (%)	24 (63.2)	55 (70.5)	0.42
ECOG 0–1, n (%)	30 (78.9)	43 (55.1)	0.01
T1–T2 stage, n (%)	26 (68.4)	25 (32.1)	<0.001
N0 disease, n (%)	22 (57.9)	22 (28.2)	0.003

Well/moderately differentiated histology, n (%)	34 (89.5)	52 (66.7)	0.01

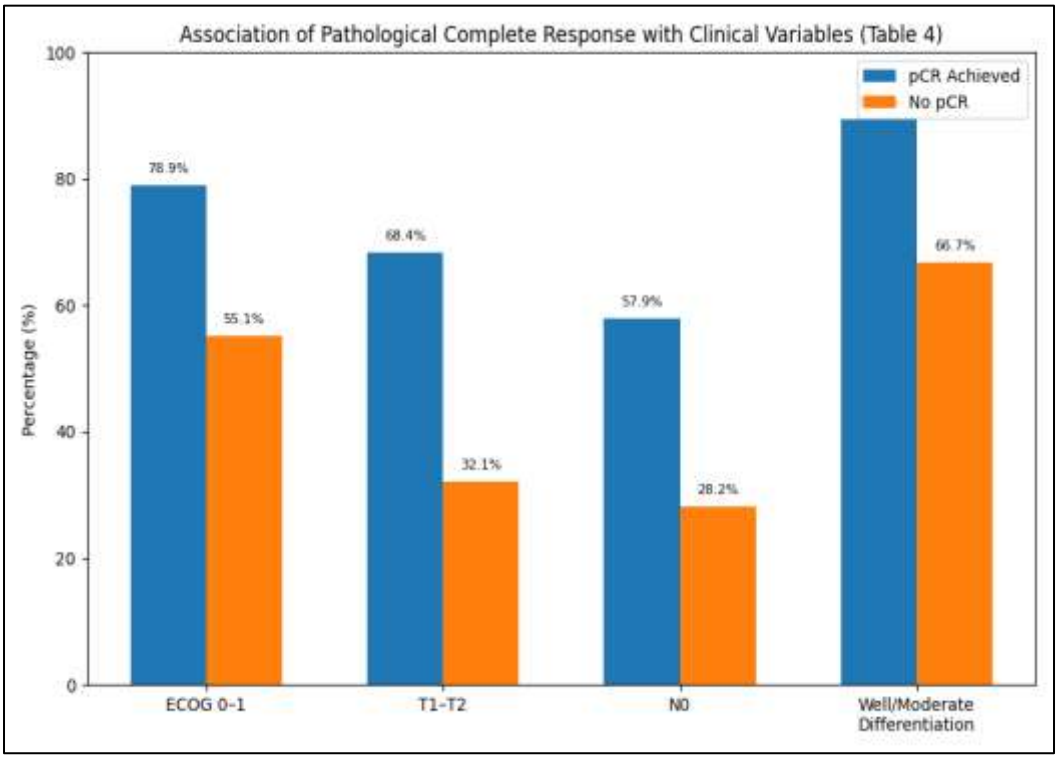

Figure 2: Association Between Clinicopathological Variables and Pathological Complete Response in Resectable Esophageal Squamous Cell Carcinoma Patients

Overall, 61 (52.6%) patients experienced treatment-related toxicity. Fatigue was the most common toxicity (42, 36.2%), followed by nausea/vomiting (34, 29.3%) and esophagitis (29, 25.0%). Hematological toxicity occurred in 19 (16.4%) patients, including neutropenia in 13 (11.2%). Treatment interruption due to toxicity occurred in 14 (12.1%), while 9 (7.8%) required hospital admission.

Table 5: Treatment-Related Toxicities During Therapy (N = 116)

Variable	n (%)
Any treatment-related toxicity	61 (52.6)
Nausea/vomiting	34 (29.3)
Esophagitis	29 (25.0)
Fatigue	42 (36.2)
Hematological toxicity	19 (16.4)
Neutropenia	13 (11.2)
Treatment interruption due to toxicity	14 (12.1)
Hospital admission due to toxicity	9 (7.8)

DISCUSSION

The aim of this study was to assess the rate of pathological complete response (pCR) in patients with resectable esophageal squamous cell carcinoma (ESCC) who received induction chemotherapy, then concurrent chemoradiotherapy and surgery. The results showed that 32.8% of the patients had pathological complete response and 87.1% had R0 resection. These results indicate a promising tumor response and good surgical results for the multimodal treatment approach in this patient population [15]. The mean age of the study population was 54.8 ± 9.6 years and the majority were male (68.1%). This age- and sex-distribution is similar to what is known about the epidemiology of esophageal squamous cell carcinoma, which tends to be more common in males, and is more likely to occur in older adults compared to young people, due to the involvement of known risk factors like tobacco use, dietary carcinogens and environmental factors. Also, the mean age of patients reported in previous studies ranged from 50 to 60 years with male predominance of more than 60% which corroborates our demographic results [16]. The staging of the patients' tumors showed that the majority of them had advanced local disease, 56.0% with T3 tumors

and 62.1% with nodal involvement. This is because the biology of esophageal cancer is very aggressive and people often don't seek care until later in the disease's course, particularly in developing nations where early detection is not common. The disease burden of similar patients was also found in previous research, with the majority of patients with esophageal squamous cell carcinoma having T3 disease and positive nodes [17]. Pathological complete response rate of 32.8% in this study is clinically significant, which suggests that the induction chemotherapy plus concurrent chemoradiotherapy is effective. Pathological complete response is a significant prognostic factor that is linked to better disease-free survival and overall survival. The pCR rate observed in our study is similar to rates seen in prior studies of esophageal squamous cell carcinoma (ESCC) with neoadjuvant multimodal treatment (NMMT), which have ranged from about 25% to 40%. This implies that induction chemotherapy could play a role in achieving good tumor regression in well-chosen patients [18]. Excellent surgical clearance was obtained after the preoperative therapy with R0 resection in 87.1% of patients. Negative resection margins are a very good predictor of good oncological outcomes and low recurrence rates. Our results also corroborate previous findings, which have shown resection rates of 80–92% after neoadjuvant chemoradiotherapy [19].

There was a significant difference between the mean ages of the patients in the pathological complete response (pCR) and non-pCR groups (51.2 ± 8.7 years vs 56.5 ± 9.8 years). The younger age may be a sign of better physiological reserve, better tolerance to the treatment, and better response of the tumor to the treatment. However, pCR was also significantly associated with better ECOG PS (78.9% of the responders had ECOG 0–1). The same factors, younger age and functional performance were found to be good predictors of treatment response response in previous studies [20]. Treatment response was also significantly affected by tumor-related factors. Achievement of pCR was significantly associated with earlier tumor stage (T1–T2), lack of nodal disease and histological differentiation. The responses of patients in T1–T2 disease were significantly higher than those with advanced tumors. In the same way, a non-neuroendocrine type of tumor with a well to moderately differentiated histology was correlated with better pathological results. Lower tumour burden and good histopathological features have been consistently associated with better treatment response in previous studies [21].

Limitations

This study has several limitations. Being a single-center prospective observational study, the findings may have limited generalizability to broader populations or other healthcare settings. The relatively modest sample size of 116 patients may restrict the statistical power for subgroup analyses and limit detection of smaller associations. The absence of a comparison group receiving alternative treatment strategies, such as concurrent chemoradiotherapy without induction chemotherapy, limits the ability to directly assess the added benefit of induction chemotherapy. Long-term outcomes such as overall survival, disease-free survival, and recurrence rates were not evaluated, which restricts assessment of the prognostic significance of pathological complete response in this cohort. Additionally, potential confounding factors including comorbidities, nutritional interventions, and variability in treatment tolerance may have influenced outcomes.

CONCLUSION

Induction chemotherapy followed by concurrent chemoradiotherapy and surgery demonstrated encouraging effectiveness in patients with resectable esophageal squamous cell carcinoma, with a pathological complete response rate of 32.8% and a high R0 resection rate of 87.1%. Younger age, better performance status, earlier tumor stage, absence of nodal involvement, and favorable histological differentiation were significantly associated with improved pathological response. Although treatment-related toxicities were common, the regimen was generally well tolerated with high treatment completion rates. This multimodal treatment approach appears to be a promising therapeutic strategy for resectable esophageal squamous cell carcinoma.

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