

Gastrointestinal Cancer

Chemoradiation with Weekly Paclitaxel and Carboplatin in Esophageal Squamous Cell Carcinoma: A Prospective Study

Deepa M. Joseph¹ Monica Irukulla Malik² Jyothi Jonnadula² Fayaz Ahmed² Deepthi Valiyaveetil²

¹Department of Radiation Oncology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

²Department of Radiation Oncology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

Address for correspondence Monica Irukulla Malik, MD, Department of Radiation Oncology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana 500082, India (e-mail: dr_monica11@yahoo.com).

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Abstract



Monica Irukulla Malik

Objective Neoadjuvant chemoradiation (CRT) using paclitaxel and carboplatin has significantly improved the survival rates in carcinoma esophagus, especially in squamous cell carcinoma (SCC). This regimen has not been adequately explored prospectively as a definitive CRT strategy. Our aim was to evaluate the efficacy, toxicity, and compliance to this regimen in a prospective setting in locally advanced esophageal SCC.

Materials and Methods Patients with locally advanced esophageal SCC were planned for definitive CRT by using weekly paclitaxel 50 mg/m² and carboplatin area under curve 2 along with radical radiotherapy to a dose of 50.4 to 54 Gy. Treatment-related toxicity was assessed by using the common terminology criteria for Adverse Events Version 4.0, and the response was assessed by using endoscopy and computed tomography (CT) 4 to 6 weeks following CRT. The pathological response was documented for those who underwent surgery.

Results Fifteen patients were included in the study, and all patients completed the planned course of radiation. The median number of chemotherapy cycles received was four. In total, 66% of the patients had delay or interruptions in chemotherapy, mostly due to neutropenia, and 66% of the patients had a clinical complete response (CR). Four patients underwent definitive esophagectomy, and the histopathology revealed pathologic CR. Overall CR rate was 80%. The median overall survival was 14 months, and 1-year survival was 57%.

Conclusion Definitive CRT in esophageal SCC using weekly paclitaxel and carboplatin was relatively well tolerated with manageable toxicities and good clinical response rates. It may potentially represent a new standard of care as definitive therapy in the management of these tumors.

Keywords

- ▶ esophageal squamous cell carcinoma
- ▶ radical chemoradiation
- ▶ weekly paclitaxel and carboplatin

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Introduction

Esophageal cancer is the eighth most common cancer worldwide and sixth in mortality among all malignancies.¹ Majority of the patients are diagnosed in advanced stages. Chemoradiation (CRT) plays an important role in the management of carcinoma esophagus: either as preoperative therapy or as definitive therapy in inoperable patients. Radiation dose of 41.4 to 54 Gy has been used in neoadjuvant or definitive settings. Historically, cisplatin and 5 fluorouracil (5 FU)-based chemotherapy has been used along with radiotherapy (RT) as the CRT regimen. Recent evidences suggest better survival, local control, and resection rates following paclitaxel- and carboplatin-based regimen.²

This study was done with an aim to assess the response to treatment and survival in patients treated with CRT by using weekly paclitaxel and carboplatin for esophageal carcinoma.

Materials and Methods

Patients aged between 18 and 75 years with histologically confirmed squamous cell carcinoma (SCC) of the esophagus or esophagogastric junction (Siewert I and II), TNM stage T1 to T4a, N0 to N2, M0, and a Karnofsky performance score of ≥ 70 with adequate bone marrow reserve, renal and hepatic function, were included in the study. Patients with metachronous primary and those who received any previous treatment for any malignancy were excluded from the study. RT was delivered on linear accelerators by three-dimensional conformal RT technique. The target volume and critical organs were contoured on the plain CT simulation images fused with contrast-enhanced CT images and positron emission tomography images whenever available. The gross tumor volume (GTV) was contoured as the contrast-enhancing tumor along with endoscopy correlation. The clinical target volume (CTV) was contoured as GTV expanded by 3 to 4 cm superiorly and inferiorly along the length of the esophagus and cardia and 1-cm radial expansion. The nodal CTV was contoured as 0.5 to 1.5 cm expansion from the nodal GTV. The celiac axis was covered for tumors of the distal esophagus or gastroesophageal junction. Supraclavicular nodes were included for the upper thoracic esophageal tumors. CTV was expanded by 0.5 cm to generate planning treatment volume (PTV). The boost PTV was created by 1 to 1.5 cm expansion from the initial GTV. Initial PTV was treated to a dose of 39.6 to 41.4 Gy at 1.8 Gy per fraction, followed by a cone-down boost to a total dose of 50.4 to 54 Gy in 1.8 Gy per fraction. Chemotherapy consisted of injection paclitaxel 50 mg/m² and injection carboplatin area under the curve (AUC) 2 administered intravenously (IV) once weekly for five to six cycles along with RT.

All patients were monitored during the course of treatment with weekly blood counts and liver and kidney function tests. Other investigations were done as clinically indicated. Treatment-related toxicities were assessed by using the National Cancer Institute. Common terminology criteria for Adverse Events Version 4.0. Treatment response was assessed by using CT scan and endoscopy at 4 to 6 weeks of post-treatment.

The pathological response was documented for those who underwent surgery. Statistical analysis was done by using SPSS version 20 software (IBM SPSS, Chicago, IL). Survival analysis was done by using the Kaplan–Meier method.

Results

A total of 15 patients were included in the study. The median age of the study population was 55 years ranging from 35 to 70 years. The study included eight females (53%) and seven males (47%). Comorbidities included hypertension in two patients, coronary artery disease in two patients, and diabetes in one. One patient had hypothyroidism and two had albinism.

The median tumor length was 6.5 cm ranging from 3.4 to 10.8 cm. Other patient and tumor characteristics are documented in **Table 1**. All patients underwent the planned course of RT without any significant interruptions. The median number of chemotherapy cycles received was four. Sixty-six percentage of the patients had delay or interruptions in chemotherapy, mostly due to neutropenia. Treatment-related toxicities are summarized in **Table 2**.

Two patients died within a month after CRT, one due to preexisting comorbidities, and the other patient developed metastatic disease. Sixty-six percentage of the patients had a clinical complete response (CR). Four patients underwent

Table 1 Patient characteristics

Characteristic	Number (%)
Age (y), median (range)	55 (35–70)
Sex, n (%)	
Males	7 (47)
Females	8 (53)
Tumor length (cm), median (range)	6.5 (3.4–10.8)
Tumor location, n (%)	
Proximal third	1 (6)
Middle third	8 (53)
Distal third	6 (40)
Clinical T-stage, n (%)	
cT1	0
cT2	1 (6)
cT3	9 (60)
cT4	5 (33)
Clinical N-stage, n (%)	
N0	7 (46)
N1	4 (26)
N2	4 (26)
N3	0
KPS performance status score, n (%)	
80–90	10 (66)
70	5 (33)

Abbreviation: KPS, Karnofsky Performance Score.

Table 2 Incidence of grade 2 or more toxicity during chemoradiation

Event	n (%)
Anorexia	2 (13)
Fatigue	7 (46)
Vomiting	7 (46)
Constipation	3 (20)
Diarrhea	3 (20)
Nausea	3 (20)
Leukopenia	11 (73)

definitive esophagectomy, and the histopathology revealed a pathologic CR. Overall CR rate was 80%. On follow-up, two patients developed progressive disease: one had liver metastasis and the other one supraclavicular metastasis. The median survival was 14 months, and overall survival (OS) at 1 year was 57%.

Discussion

Historically, surgery was the mainstay of treatment for esophageal cancers. However, the outcomes were dismal with very poor survival rates.³ From 2001 to 2007, the overall 5-year survival rate for esophageal cancer was reported as 19%.⁴ RT alone also resulted in poor control rates with no long-term survival.⁵ CRT has been explored as a part of trimodality therapy with the aim of improving outcomes. One of the most important initial experiences with CRT for esophageal cancer was described by Herskovic et al.⁶ Their protocol delivered radiation to a large field in 2 Gy fractions to a total dose of 30 Gy along with concomitant 5-FU/cisplatin chemotherapy, followed by a 20 Gy boost to a smaller field along with mitomycin C and bleomycin, which was later replaced with 5 FU and cisplatin. This small study of 22 patients showed a median survival of 22 months. This became the basis for the phase III RTOG 8501 trial comparing RT alone versus CRT, which showed a survival advantage with combined modality arm.⁵ The RT fields in the CRT arm included the entire esophagus in the initial 30 Gy and a boost of 20 Gy to 5 cm above and below the demonstrable tumor. Subsequently, the intergroup 0123 trial used a smaller RT field of 5 cm above and below the tumor and 2 cm radial margin. This trial established the radiation dose of 50.4 Gy in 1.8 Gy per fraction as the standard dose in CRT of carcinoma esophagus.⁷

Two phase III randomized trials have examined definitive CRT against CRT followed by surgery.^{8,9} Both these trials did not report any significant difference in OS. The French FFCD 9102 trial using 5 FU and cisplatin reported higher local control (65 vs. 57%, $p < 0.05$), and fewer stents required (5 vs. 32%, $p < 0.001$) trimodality arm compared with CRT. In the German trial, there was a higher rate of 2-year freedom from local progression (64 vs. 41%, $p = 0.003$) when the surgery was added. This trial used cisplatin and etoposide as concurrent chemotherapy.

Multiple phase II studies have evaluated paclitaxel-based chemoradiotherapy regimens in esophageal cancer with results comparable to 5 FU-based regimen with lower toxicity.^{10,11} The standard treatment of operable esophageal cancer now is trimodality treatment using neoadjuvant CRT followed by surgery. CALGB 9781 randomly assigned 56 patients to either esophagectomy with node dissection alone or CRT followed by esophagectomy with node dissection. CRT consisted of cisplatin 100 mg/m² and FU 1000 mg/m²/d for 4 days on weeks 1 and 5 concurrent with radiation therapy (50.4 Gy total: 1.8 Gy/fraction over 5.6 weeks). This trial was closed due to poor accrual. Five-year survival was 39% versus 16% in favor of trimodality therapy.¹² A meta-analysis by GebSKI et al also showed a survival advantage of neoadjuvant CRT.¹³

Recently, results of two large phase III randomized trials have been published regarding the use of neoadjuvant CRT with conflicting outcomes.^{2,14} The French trial included 195 patients from 30 centers randomly assigned to surgery versus CRT followed by surgery. RT dose was 45 Gy in 25 fractions over 5 weeks with two courses of concomitant chemotherapy composed of FU 800 mg/m² and cisplatin 75 mg/m². Compared with surgery alone, neoadjuvant CRT with cisplatin plus FU did not improve R0 resection rate or survival but enhanced postoperative mortality in patients with stage I or II esophageal cancers. The ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) trial included 368 patients randomized between neoadjuvant chemoradiotherapy plus surgery versus surgery alone. CRT consisted of 41.4 Gy in 1.8 Gy per fraction along with paclitaxel 50 mg/m² and carboplatin AUC 2 administered IV weekly. After a median follow-up of 84.1 months, there was a significant improvement in median OS (48.6 vs. 24 months) and R0 resection rates in those receiving neoadjuvant CRT. It was noteworthy that a greater benefit was observed in patients with SCC versus adenocarcinoma (median OS 81.6 vs. 43.2 months).

There are no large prospective series using paclitaxel and carboplatin in definitive CRT in carcinoma esophagus. There are few reports of small series using this regimen in definitive CRT.¹⁵⁻¹⁷ In a retrospective analysis by Noronha et al, the median progression free survival was 11 months and median OS was 19 months with manageable toxicity.¹⁸ All patients in our study were able to receive the planned dose of radiation of 50.4 to 54 Gy. Majority of our patients achieved complete remission with CRT using weekly paclitaxel and carboplatin. All the patients who underwent surgery had a complete pathological response. This demonstrates that this regimen is highly effective with a good clinical and pathological response and may obviate the need for subsequent surgery, especially in SCC.

Conclusion

Emerging evidence suggests that CRT may be the most effective treatment strategy for locally advanced SCC of the esophagus. CRT using weekly paclitaxel and carboplatin

was relatively well tolerated and resulted in a high CR rate in locally advanced SCC of the esophagus. It may potentially represent a new standard of care as definitive therapy in the management of these tumors.

Funding

None.

Conflict of Interest

None declared.

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