UDC 612.3
DOI: 10.15587/2519-4798.2023.274476

STUDY OF CONSOLIDATION CHEMOTHERAPY AFTER DEFINITIVE CHEMORADIATION IN LOCALLY ADVANCED CARCINOMA ESOPHAGUS IN A TERTIARY CARE HOSPITAL

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Concurrent chemoradiation (CCRT) is considered the standard of care in locally advanced and inoperable carcinoma oesophagus patients. However, the majority of these patients have residual disease after completion of CCRT, and there are no definitive treatment guidelines for the management of the residual disease. Reports on consolidation chemotherapy for patients with oesophagal cancer after definitive CCRT are rare and have shown mixed results.

***The aim** of this study was to see the effects of consolidation chemotherapy in patients of CCRT who had residual disease and were not surgical candidates and also monitor its side effects.*

***Material and methods:** It was a prospective interventional protocol over 2 years where patients received 4 cycles of consolidation chemotherapy post-CCRT. These patients were followed after completion of chemotherapy for response, toxicity and survival.*

***Results:** 45 patients were initially enrolled for the study, histopathologically proven carcinoma of the oesophagus, out of which 30 patients finally received the full course of treatment and were available for final assessment. After consolidation chemotherapy, 23 (76.7 %) patients had a complete response, 3 (10 %) had a partial response, and 4 (13.3 %) had stable disease. There was no progression of the disease during treatment. The overall treatment protocol was well tolerated by all the patients. There were no grade IV toxicities. On follow-up till the compilation of this data, 23 (76.6 %) of the patients were alive, and 7 (23.3 %) died (disease-related events). Out of these 7 patients, 4 patients had a local failure, and 3 patients developed distant metastasis in the form of brain and liver metastasis.*

***Conclusion:** Consolidation chemotherapy after concurrent chemoradiation in locally advanced, inoperable carcinoma oesophagus is a well-tolerable protocol with high chances of complete response rates*

***Keywords**: ca oesophagus, the squamous cell ca, consolidation chemotherapy, CCRT, Pactitaxel, Carboplatin, Esophagitis, Chemo induced neurotoxicity*

How to cite:
Ahmad, W., Najmi, A. M., Wani, N., Wani, S. Q., Banday, S., Nasreen, S. (2023). Study of consolidation chemotherapy after definitive chemoradiation in locally advanced carcinoma esophagus in a tertiary care hospital. ScienceRise: Medical Science, 1 (52), 25–32. doi: http://doi.org/10.15587/2519-4798.2023.274476

1. Introduction

Cancer is a major concern in all nations of the world. About 19 million people are diagnosed with cancer, and more than 50 % die due to various cancers every year. Oesophagal cancer is the ninth most common cancer and the sixth leading cause of cancer-related deaths worldwide [1]. India has an age-standardised incidence rate (ASR) of 6.1 per 100,000 population for males and 3.4 per 100,000 population for females [1]. A very high incidence of oesophageal cancers has been reported in the North-East region of India. This is part of an oesophageal "cancer belt," which extends from northeast China to the Middle East. Cancer oesophagus cancer is more prevalent in less developed Asian countries [2]. The Kashmir valley is yet another high-incidence area in the country. As per the hospital-based cancer registry (HBCR), SKIMS Esophagus cancer has been one of the leading cancers in both genders, and in 2021 it ranked as 3rd overall malignancy in males.

Oesophageal cancer has a high probability of metastasis as well as low 5-year survival rates (ranging from 15–25 %) [3]. Although outcomes of patients with locally advanced disease have improved, survival is still dismal in most patients [4]. The main reason for poor survival is the disease's late presentation and the oesophagus's rich lymphatic network. The significant factors leading to survival include male gender, not resected, longer wait time, low socioeconomic status and old [5].

The National Comprehensive Cancer Network guidelines recommend definitive chemoradiotherapy for only medically unfit patients for surgery, those with unresectable tumours, and those with cervical oesophagal

lesions. However, there are no definitive treatment guidelines after concurrent chemoradiation. The majority of these patients have residual disease post-CCRT and are not operable but fit for chemotherapy. Consolidation chemotherapy after initial treatment has been attempted at many centres to improve cancer patient outcomes and has shown efficacy in some cancers, such as cervical and non-small-cell lung cancer. However, reports on consolidation chemotherapy for patients with oesophagal cancer after definitive chemoradiation is rare and have shown mixed results.

In a few retrospective trials, it has been seen that, in these patients who receive consolidation chemotherapy, there is an overall survival benefit with an acceptable toxicity profile. But consolidation chemotherapy can lead to adverse effects also, and care must be taken so that the benefits of chemo outweigh the toxicities.

Therefore, our aim was to see the overall response of consolidation chemotherapy after concurrent chemoradiation in patients who are not surgical candidates and monitor side effects due to consolidation chemotherapy.

2. Materials and methods

A prospective interventional study was conducted in the department of radiation oncology and department of gastroenterology, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, over a period of 2 years (2020–2021). The aim of the study was to see the effects of consolidation chemotherapy in patients after definitive concurrent chemoradiation in locally advanced oesophagal carcinoma in terms of overall response, toxicity and survival. Patients of age 18 to 65 years, with performance status <2 (0,1), histologically proven Squamous cell carcinoma oesophagus, with normal baseline investigations {CBC, KFT, LFT}, the locally advanced disease having residual disease after concurrent chemoradiation, and who were nonsurgical candidates were included. Patients with abnormal metabolic profile CBC/LFT/KFT, comorbidities (uncontrolled Diabetes or active cardiac disease), Metastatic disease (Stage IV), ECOG performance status ≥2, previous H/O malignancy / thoracic irradiation, or who underwent surgical resection were excluded. The selected patients were evaluated with complete history, physical examination [Height/Weight/BSA], Baseline investigations (CBC, LFT, KFT, Creatinine clearance), Barium swallow X-ray, Esophago-duodenoscopy with biopsy of the growth, CECT Neck/ chest/Abdomen, Cardiology clearance for Chemotherapy, Bone scan/MRI brain /PET scan wherever indicated.

Bioethics: the study was duly approved by the institutional ethics committee (IEC) of Sheri- Kashmir Institute of Medical Sciences, Soura Srinagar J&K India, vide protocol number RP-61/2019, dated Dec 23 2020.

All selected patients received 4 cycles of consolidation chemotherapy after completion of concurrent chemoradiotherapy.

Radiotherapy protocol:

A total dose of 50.4Gy was given to the primary tumour and involved lymph nodes at 2Gy-2.08Gy/fraction, 5 fractions a week over a period of 5 weeks. In the first phase 40 Gy was given by AP/PA portals and the dose to the primary tumour was escalated by oblique portals to spare the spinal cord. All patients were treated using a telecobalt unit; Theratron 780E or Bhabhatron II.

Chemotherapy protocol:

A concurrent chemotherapy regimen was given using paclitaxel 50 mg/m^2 intravenously and Carboplatin (AUC2) every week for 5 weeks. f/b four cycles of consolidation chemotherapy, Paclitaxel 175–200 mg/m^2 day 1 and carboplatin (AUC 5-6) every three weeks. The premedication includes antiemetic, 5-HT3 antagonist (ondansetron), antihistaminic (pheniramine maleate), H2 blockers (ranitidine) and steroids (dexamethasone).

All patients were reviewed weekly during concurrent chemoradiation to assess treatment-induced toxicities per CTCAE criteria V 5.0 guidelines. After completion of concurrent chemoradiation, patients were assessed for response with Esophago-duodenoscopy ± Biopsy and CECT chest/abdomen after 4 weeks. Patients with residual disease and benefiting from our inclusion criteria were taken for consolidation chemotherapy after having written consent. Patients were also assessed for toxicity during and after consolidation chemotherapy as per CTCAE guidelines. After completion of consolidation chemotherapy, patients were again assessed for response with oesophagus-duodenoscopy ±biopsy and CECT chest/Abd. Thereafter patients were on regular follow-up with history, complete physical examination and investigation as required, every 3 to 6 months for the first year post consolidation chemotherapy and every 3 months afterwards.

Statistical analysis: The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to the data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean±SD, and categorical variables were summarised as frequencies and percentages. χ^2 test or Fisher's exact test, whichever is appropriate, was applied to compare categorical variables. A P-value of less than 0.05 was considered statistically significant. All P-values were two-tailed.

3. Results

45 patients were initially enrolled for the study, histopathologically proven carcinoma of the oesophagus. Out of 45 patients, 5 did not consent to consolidation chemotherapy and hence were excluded. 5 patients received concurrent chemoradiation and then went for surgery and hence were excluded, 3 patients defaulted during consolidation chemotherapy, and 2 patients were not available for assessment. 30 patients finally received a full course of treatment and were available for final assessment.

The characteristics of the study patients are shown in Table 1. Out of 30 patients, most of the patients were in the age group of 60–69 (43 %), with mean age (±SD) of 56.2 years (±7.96). Male to female ratio was 2:1, with males comprising 20 (66.7 %) of patients. 27 (90 %) of patients were from rural areas (Table 1).

Table 1

Patient characteristics

AGE (Yr)		<50	4 (13.3 %)
		50–59	12 (40 %)
		60–69	13 (43.3 %)
		≥70	1 (3.3 %)
GENDER		Male	20 (66.7 %)
		Female	10 (33.3 %)
ADDRESS		Rural	27 (90 %)
		Urban	3 (10 %)
SYMPTOMS	Dysphagia (grade)	1	2 (6.6 %)
		2	8 (26.6 %)
		3	15 (50 %)
		4	5 (16.6 %)
	Pain abdomen		6 (20 %)
	Epigastric discomfort		3 (10 %)
	Weight loss		15(50 %)
	Loss of appetite		20 (66 %)
	Generalised weakness		25 (83 %)
Location of lesion	Cervical oesophagus		14 (46.7 %)
	Thoracic Esophagus		14 (46.7 %)
	Lower oesophagus		2 (6.7 %)
Size of lesion	< 5 cm		13 (43 %)
	≥ 5 cm		17 (57 %)
Histological grade	Well-differentiated		8 (26.7 %)
	Moderately differentiated		16 (53.3 %)
	Poorly differentiated		6 (20 %)
ECOG Performance status	0		13 (43.3 %)
	1		17 (56.7 %)

A risk factor assessment was done. Out of 30 patients, 20 (66.7 %) were male, 22 (73.3 %) had a history of smoking, 26 (86.3 %) were in the age group (45–70), 20 (66.7 %) belonged to rural areas, and 18 (60 %) were from the low socioeconomic background. All the patients presented with dysphagia as their main complaint, with most having Grade 3 dysphagia 15 (50 %). Patients were equally distributed between the upper and middle oesophagus, with 14 each. Of the middle oesophagal location, 6 each were in the middle 1/3rd and lower 1/3rd of the middle oesophagus, and the remaining 2 patients were in the upper 1/3rd of the middle oesophagus. Most of the patients had lesions measuring ≥5 with no statistical significance. The length of the lesion was determined by a CECT scan.

After completion of consolidation chemotherapy, we assessed the patient for response with CECT /Endoscopy. 23 (76.7 %) had a complete response, 3 (10 %) had a partial response and 4 (13.3 %) had stable disease. There was no disease progression during treatment (Table 2). The comparison of response after completion of consolidation chemotherapy with respect to its location and grade of the lesion with no statistical significance (Table 2).

Table 2

Post-consolidation response with respect to location and grade of disease in study patients

Overall response (N=30)			Complete response Number (percentage)	Partial response Number (percentage)	Stable disease Number (percentage)	P valve
			23 (76.7 %)	3 (10 %)	4 (13.3 %)	
Location of lesion	Cervical oesophagus (N-14)		10 (71.4 %)	1 (7.1 %)	3 (21.4 %)	0.261
	Thoracic oesophagus (N-14)	Upper 1/3	6 (100 %)	0	0	
		Middle 1/3	5 (83.3 %)	0	1 (16.7 %)	
		Lower 1/3	1 (50.0 %)	1 (50.0 %)	0	
	Lower oesophagus (N-2)		1 (50.0 %)	1 (50.0 %)	0	
	Total		23 (76.7 %)	3 (10.0 %)	4 (13.3 %)	
Grade of tumour	Well-differentiated (WD) (N=8)		8 (100 %)	0	0	0.142
	Moderately differentiated (MD) (N=16)		12 (75.0 %)	1 (6.3 %)	3 (18.8 %)	
	poorly differentiated (PD) (N=6)		3 (50.0 %)	2 (33.3 %)	1 (16.7 %)	
	Total (N=30)		23	3	4	

Post CCRT, 8 (26.7 %) patients had haematological toxicities, 7 patients (23.3 %) had esophagitis or dry mouth, 3 (10 %) developed vomiting, and 6 (20 %) patients developed neurotoxicity but none with grade 3 toxicity.

Post-consolidation chemotherapy patients experienced various kinds of toxicities; the most noted was neurotoxicity, which was seen in 13 (43.3 %) patients in the form of peripheral sensory neuropathy, in which 7 (23.3 %) patients had grade I toxicity, 4 (13.3 %) patients with grade II and 2 (6.7 %) patients had grade III neurotoxicity. 10 (33.3 %) patients had haematological toxicities in the form of neutropenia, with 4 (13.3 %) patients each suffering from grade I and grade II toxicity, and 2 (6.7 %) grade III toxicity, which required hospitalisation. 4 patients experienced vomiting and diarrhoea, grade I in 1 (3.3 %) and grade II in 3 (10 %) patients. One patient had extravasation of the drug and developed grade III skin toxicity, and chemo was interrupted for one week. Patients with grade III toxicities required hospitalisation, and there was one week of interruption in treatment in 5 (16.6 %) of patients. The treatment protocol was well tolerated by all the patients. There were no grade IV toxicities of any symptoms, and the patient tolerated consolidation chemotherapy well (Table 3).

The grade of toxicity was correlated with ECOG performance status. ECOG PS 0 experienced fewer toxicities than ECOG PS 1 patient, with no statistical significance [P value 0.406] (Table 4).

Table 3

Showing various toxicities post consolidation in study patients

Toxicity		Number	Percentage
Haematological toxicity	Grade 1	4	13.3
	Grade 2	4	13.3
	Grade 3	2	6.7
	Grade 4	0	0.0
	Grade 5	0	0.0
Neuro toxicity	Grade 1	7	23.3
	Grade 2	4	13.3
	Grade 3	2	6.7
	Grade 4	0	0.0
	Grade 5	0	0.0
Vomiting/diarrhoea	Grade 1	1	3.3
	Grade 2	3	10
	Grade 3	0	0.0
	Grade 4	0	0.0
	Grade 5	0	0.0

Table 4

Toxicity profile according to ECOG performance status

Toxicity	ECOG 0		ECOG 1	
	number	percentage	number	percentage
No toxicity	2	15.4	1	5.9
Grade 1	7	53.8	7	41.2
Grade 2	2	15.4	6	35.3
Grade 3	2	15.4	3	17.6
Grade 4	0	0.0	0	0.0
Total	13	100	17	100
χ^2=2.906; P-value=0.406				

Patients were on regular follow-ups after the completion of consolidation chemotherapy. The longest follow-up was 26 months, with a median follow-up period of 15 months (Table 5). Till the compilation of this data, 23 (76.6 %) of the patients were alive, and 7 (23.3 %) died, all the 7-patient died due to disease-related events (Table 5). Out of these 7 patients, 4 patients had a local failure, and 3 patients developed distant metastasis in the form of brain and liver metastasis.

During follow-up, we correlated local and distant failure with respect to the ECOG performance at presentation (P=0.851), response with treatment (P=0.315) and grade of the tumour (P=0.465) with no statistical significance (Table 6).

Table 5

Follow-up of study patients

	Months	number	percentage
Follow up in months	<12	4	13.3
	12–24	23	76.7
	>24	3	10
Patient status at follow up	Alive	23	76.7
	Dead	7	23.3

Table 6

Progression of disease with regards to ECOG status, response achieved & grade of the tumour

Progression of disease (N=30)		Local progression	Distant progression	Overall progression	P valve
		5 (16.6 %)	3 (37.5 %)	8 (26.6 %)	
ECOG	0	2 (15.3 %)	1 (7.6 %)	3 (23 %)	0.851
	1	3 (17.6 %)	2 (11.7 %)	5 (29.3 %)	
Response	Complete (N=23)	1 (4.3 %)	2 (8.7 %)	3 (13 %)	0.315
	Partial (N=3)	2 (66.6 %)	0	2 (66.6 %)	
	Stable (N=4)	2 (50 %)	1 (25 %)	3 (75 %)	
Grade	WD (N=8)	0	0	0	0.465
	MD (N=16)	2 (12.5 %)	2 (12.5 %)	4 (25 %)	
	PD (N=6)	3 (50 %)	1 (16.7 %)	4 (66 %)	

4. Discussion

The overall five-year cure rates for patients with carcinoma oesophagus have not changed significantly over the past few decades, despite the excellent progress made in supportive care, surgical technique, radiotherapy and chemotherapy. The reason is oesophagal cancers are rarely diagnosed early enough to permit curative treatment. The primary therapy for oesophagal cancer can be surgical or non-surgical. Patients with medical contraindications for surgery, primary unresectable or metastatic disease, and low-performance status (PS) are commonly selected for nonsurgical therapy.

The 3-year survival rate for patients with locally advanced oesophagal cancer after chemoradiotherapy (CRT) and/or surgery has typically been in the range of 15 % to 30 %. Neo Adjuvant concurrent chemoradiation is currently considered standard therapy for patients with locally advanced oesophageal cancer. The long-term results from the updated landmark CROSS [6] trial showed that the preoperative chemoradiotherapy group offers a significant OS benefit over surgery alone. For locally advanced oesophagal cancer, cisplatin-based chemoradiation has been considered the standard of care, as shown in RTOG 85-01 and INT 0123 trials. However, even after definitive chemoradiation therapy, 5-year survival rates are poor (20.2 %), necessitating the need for newer treatment strategies [7].

Consolidation chemotherapy after concurrent chemoradiation is intended to improve outcomes and has shown good responses in some cancers, such as cervical and non-small-cell lung cancer. However, reports on consolidation chemotherapy for patients with oesophagal cancer after definitive concurrent chemoradiation is meagre.

Studies have shown that consolidation chemotherapy can improve median overall survival and progression-free survival after completion of concurrent chemoradiation. The most noted study was done by Sheng-Xi Wu [8] in China, and another study by Zongxing Zhao [9].

We conducted a single-arm study on patients having residual disease after CCRT and gave them consolidation chemotherapy to see the effects in terms of toxicity, response and survival.

In this study, 45 patients of carcinoma oesophagus were taken who had residual disease after CCRT. Out of these, only 30 patients finally received the full course of treatment and were available for final assessment.

Out of 30 patients, 13 (43 %) were in the age group of 60–69, 12 (40 %) were in the age group of 40–59, with a mean age of 56.2±7.96. This was consistent with the study by the American Cancer Society, Cancer Facts & Figures 2016 [10]. Oesophageal cancer is most frequently diagnosed in people aged 64–74 years, with a median age of 6 years at diagnosis.

In our study, most of the patients were from rural areas 27 (90 %), with the majority coming from low socioeconomic backgrounds. A low socioeconomic class is associated with an increased risk of oesophagal squamous cell carcinoma. A study showed an interplay among many factors, such as poor nutritional status, a diet lacking in fresh food, fruit and vegetables, and poor oral hygiene and tooth loss [11], which is responsible for oesophagal squamous cell carcinoma.

In Kashmir valley, people generally consume a lot of hot beverages and spices. In our study, 15 (50 %) of the population gave a history of excessive hot beverages, and 12 (40 %) patients consumed excessive spices. 15 (50 %) of the population were cigarette smokers, and 6 (20 %) were hookah smokers. Consumption of hot food and beverages is associated with an increased risk of oesophagal cancer, particularly squamous cell cancer [12].

The male-to-female ratio was 2:1 in our study, which was consistent with a study conducted by Vizcaino AP et al. [13] in which the incidence of Ca oesophagus was 3 times higher in males than females.

Dysphagia is the commonest symptom in carcinoma oesophagus, and same was the case in our study, with all 30 patients presenting with dysphagia. The dysphagia was grade I in 2 (6.7 %) patients, Grade II in 8 (26.7 %) patients, Grade III in 15(50 %) of patients and grade IV in 5 (16.6 %) patients at the time of presentation. This was compared to a study done in Tanzania which found Grade I dysphagia at presentation in 0 %, Grade II in 4.6 %, Grade III in 14.9 % and Grade IV in 43 % [14].

Squamous cell histology is the commonest subtype of Ca oesophagus in our setup. Histopathologically, 16 (53.3 %) patients had moderately differentiated grades, followed by 8 (26.7 %) patients with well-differentiated and the remaining 6 (20 %) patients had poorly differentiated grades. Worldwide squamous cell carcinoma is the predominant histological type, although adenocarcinoma is seen more in the western population [15].

Patients with ECOG ≥2 were not included in our study as these patients had to receive concurrent chemoradiotherapy followed by consolidation chemotherapy.

Patients were treated with 50.4 GY radiation concurrent with chemotherapy as per the landmark INT-0123 trial [16]. Although chemotherapeutic agents used were pacli/carbo instead of cis/5 FU.

All selected patients received 4 cycles of consolidation chemotherapy after completion of concurrent chemoradiotherapy. In addition, patients were followed up with physical examination, endoscopy, and contrast-enhanced CT, 1 month after the completion of CRT.

After receiving treatment, most patients had a significant response in symptoms. In addition, there was an improvement in the grade of dysphagia, which improved after treatment in >90 % of patients to grade 0–1. The improvement in symptoms and dysphagia was in comparison with historical data (70 to 75 % improvement) [16].

The consolidation chemotherapy was well tolerated in all our patients. Treatment interruption was seen only in 5 (16.6 %) of patients. Post consolidation chemotherapy, the commonest toxicity experienced was neurotoxicity which was seen in 13 (43.3 %) patients in the form of peripheral sensory neuropathy, with most of the patients having grade I toxicity 7 (23.3 %) patients, followed by 4 (13.3 %) patients with grade II and 2 (6.7 %) patients had grade III neurotoxicity.

Haematological toxicity in the form of neutropenia was experienced by 10 (33.3 %) patients, with 4 (13.3 %) patients each suffering from grade I and grade II toxicity and 2 (6.7) patients had grade III toxicity which required hospitalisation. 4 patients experienced vomiting and diarrhoea, it was of grade I in 1 (3.3 %) patients and grade II in 3 (10 %) patients. The toxicities were comparable, and there was no death related to toxicity. There is fewer data on toxicities related to consolidation chemotherapy in carcinoma oesophagus. In a study by Sheng, et al., consolidation chemotherapy was given after definitive concurrent chemoradiation. They reported grade 3 or greater toxicities during consolidation chemotherapy in the form of neutropenia in 17.9 %, nausea in 16.4 % and stomatitis in 10.4 % patients [17].

Obviously, it was difficult to ascertain pathological response in the absence of surgical specimens. We based our complete response on the fact that no lesion was seen on both EGD and CECT after the completion of consolidation chemotherapy. 23 (76.7 %) patients had complete responses with no lesion in both EGD and CECT. 3 (10 %) patients had a partial response with a reduction in the ,lesion size and 4 (13.3 %) of the patient had stable disease. There was no progression of the disease during treatment.

We did a multivariate analysis of various factors. We found that patients with a lesion in the cervical oesophagus and upper and middle parts of the thoracic oesophagus had a better response than a lesion in the lower half of the oesophagus. This was consistent with Chen Y et al. [18], who revealed that the overall survival of patients with primary tumours located in the middle/lower thoracic oesophagus is poorer than those with cervical/upper thoracic disease when both groups were treated with chemoradiotherapy possibly due to poorer clinical response for a lesion in the lower 1/3rd.

In our study, patients with well-differentiated and moderately differentiated tumour grades responded better than poorly differentiated ones. All 8 (100 %) patients had well-differentiated histology showing complete response. And in case of moderately differentiated grade out of 16 patients 12 (75 %) patients showed complete response, 1 (6.3 %) partial response, and 3 (18.8 %) had stable disease. Poorly differentiated grade had 6 patients in total and out of which 3 (50 %) had a complete response, 2 (33.3 %) with partial response and 1 (16.6 %) had a stable disease. However, this was not statistically significant. As per various studies, it is seen that poorly differentiated histology has a propensity for nodal and distant metastasis and hence has a poor prognosis, as shown by the study by Dashan et al. [19]

At 1 year of follow-up, 23 (76.6 %) of the study patients were alive, and 7 (23.4 %) patients died due to disease-related events. Out of 30 patients, 8 (16.6 %) patients had progression of disease after consolidation chemotherapy in the form of local recurrence, which was seen in 5 (16.6 %), documented with endoscopy and biopsy, 3 (10 %) patients had distant metastasis in the form of brain and liver metastasis There is no direct prospective trial to see the effect of consolidation chemotherapy in carcinoma oesophagus. However, a retrospective study by Sheng-Xi Wu et al. 1 showed overall survival benefits [8]. The median progression-free survival times were 33.0 months and 18.0 months in the consolidation chemotherapy and control groups, respectively. No differences in total progression events were observed between the two groups, with 94 (66.2 %) of 142 occurring in the control group and 36 (53.7 %) of 67 in the consolidation chemotherapy group. A similar finding was observed for local recurrence events, with 32 of 142 (22.5 %) occurring in the control group versus 21 (31.3 %) of 67 in the consolidation chemotherapy group. However, fewer patients had distant metastases in the consolidation chemotherapy group than in the control group (15 [22.4 %] of 67 versus 62 [43.7 %] of 142). The median overall survival times were 53.4 months and 27.0 months for the consolidation chemotherapy and control groups, respectively. The 1-, 2- and 3-year overall survival rates were 67.3 %, 38.9 %, and 30.2 % in the consolidation chemotherapy group and 62.8 %, 34.4 %, and 26.4 % in the control group, respectively. But in the said retrospective study, the follow-up period was over 2 years.

Although the number was less, we compared these patients who progressed during follow-up with the type of response. We observed that disease progression after consolidation chemotherapy was inversely proportional to the response seen. In complete responders, 1 (4.3 %) patient had local recurrence and 2 (8.7 %) had distant metastasis. In partial responders, 2 (66.6 %) patients developed local oesophagal recurrence. In patients with stable disease, 2 (50 %) patients progressed with oesophagal recurrence and 1 (25 %) had distant metastasis in the form of liver metastasis. None was statistically significant with a P-value>0.05. This was comparable to a retrospective study by Zongxing Zhao et [9], who found that 3-year OS rates were 57.1 % and 28.7 % for good responders and poor responders, respectively, while their median survival times were 46.0 and 21.6 months,

respectively. The 3-year PFS rates were 28.0 % for good responders and 20.6 % for poor responders. Studies have also documented better results of consolidation chemotherapy in patients who had not shown satisfactory responses to initial definitive treatment. Our study included only patients with residual disease post concurrent chemoradiation.

During follow-up, we also compared the disease's progression with the differentiation grade. All 8 patients with well-differentiated histology were complete responders and had no distant or local failure until the last follow-up. Of 16 patients with moderately differentiated histology, 2 (12.5 %) had local and distant metastasis. Out of 6 patients with poorly differentiated histology 3 (50 %) patients have a local recurrence and 1 (16.6 %) patient presented with distant metastasis ($p<0.05$).

Out of 13 patients with ECOG-0 2 (15.3 %) had local failures, and 1 (7.6 %) had distant failures. Similarly, out of 17 patients with ECOG-1 5 (29.4 %) had a local failure. P value was 0.851, and the results were not significant.

The limitation of our study was that the period was short to evaluate differences in late toxicity, long-term efficacy, the pattern of disease recurrence and disease-free survival after completion of consolidation chemotherapy. Second, this study was conducted at a single centre with relatively few patients. However, long-term follow-up and large randomised trials are needed to determine the overall survival, disease-free survival, long-term toxicities and failure patterns in these patients to draw definitive conclusions.

Prospects for further research. A randomised controlled trial with a larger sample size and a more extensive follow-up period is needed to establish survival benefits in this group of patients.

5. Conclusion

1. The locally advanced disease prognosis remains poor, with a meagre 5- year survival rate. There is still no established treatment protocol for patients who are not surgical candidates after concurrent chemoradiation, especially for patients with residual disease.

2. In our study, we found that for patients with residual disease after concurrent chemoradiotherapy, consolidation chemotherapy is a decent option with good response rates and an acceptable toxicity profile, despite the small sample size in our study.

3. Benefits with consolidation chemotherapy were comparatively better in cervical and upper thoracic lesions, well-differentiated histology, and ECOG-0.

In patients with residual disease after concurrent chemoradiotherapy, consolidation chemotherapy is a decent option with good response rates and acceptable toxicity profile. The benefits with consolidation chemotherapy were comparatively better in cervical and upper thoracic lesions, well-differentiated histology and ECOG-0.

Conflict of interest

The authors declare that there is no conflict of interest in relation to this paper, as well as the published research results, including the financial aspects of conducting the research, obtaining and using its results, as well as any non-financial personal relationships.

Funding

The study was performed without financial support.

Data availability

The data of these patients are stored in the files, which are maintained confidentially in the medical record section of our hospital (a tertiary care centre). These files get updated at every patient visit to the hospital.

Acknowledgements

Departments of Medical Gastroenterology/ Medical Oncology/ Surgical Oncology/ Medical Physics, SKIMS.

References

1. GLOBOCON (2020). World Health Organization. Available at: https://gco.iarc.fr/today

2. Pakzad, R., Mohammadian-Hafshejani, A., Khosravi, B., Soltani, S., Pakzad, I., Mohammadian, M. et al. The incidence and mortality of esophageal cancer and their relationship to development in Asia. Annals of Translational Medicine, 4 (2), 29.

3. Tustumi, F., Kimura, C. M. S., Takeda, F. R., Uema, R. H., Salum, R. A. A., Ribeiro-Junior, U., Cecconello, I. (2016). Prognostic factors and survival analysis in esophageal carcinoma. ABCD. Arquivos Brasileiros de Cirurgia Digestiva (São Paulo), 29 (3), 138–141. doi: https://doi.org/10.1590/0102-6720201600030003

4. Noronha, V., Simha, V., Patil, V., Joshi, A., Prabhash, K. (2019). Role of palliative chemotherapy and targeted therapy in advanced esophageal and gastroesophageal junction cancers. Cancer Research, Statistics, and Treatment, 2 (2), 172–181. doi: https://doi.org/10.4103/crst.crst_10_19

5. Zarean, E., Mahmoudi, M., Azimi, T., Amini, P. (2018). Determining Overall Survival and Risk Factors in Esophageal Cancer Using Censored Quantile Regression. Asian Pacific Journal of Cancer Prevention, 19 (11), 3081–3086. doi: https://doi.org/10.31557/apjcp.2018.19.11.3081

6. Shapiro, J., van Lanschot, J. J. B., Hulshof, M. C. C. M., van Hagen, P., van Berge Henegouwen, M. I., Wijnhoven, B. P. L. et al. (2015). Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. The Lancet Oncology, 16 (9), 1090–1098. doi: https://doi.org/10.1016/s1470-2045(15)00040-6

7. Ochi, M., Murakami, Y., Nishibuchi, I., Kubo, K., Imano, N., Takeuchi, Y. et al. (2020). Long-term results of definitive chemoradiotherapy for unresectable locally advanced esophageal squamous cell carcinoma. Journal of Radiation Research, 62 (1), 142–148. doi: https://doi.org/10.1093/jrr/rraa110

8. Wu, S.-X., Li, X.-Y., Xu, H.-Y., Xu, Q.-N., Luo, H.-S., Du, Z.-S. et al. (2017). Effect of consolidation chemotherapy following definitive chemoradiotherapy in patients with esophageal squamous cell cancer. Scientific Reports, 7 (1). doi: https://doi.org/10.1038/s41598-017-17254-9

9. Zhao, Z., Zhang, Y., Wang, X., Geng, X., Zhu, L., Li, M. (2020). Clinical response to chemoradiotherapy in esophageal carcinoma is associated with survival and benefit of consolidation chemotherapy. Cancer Medicine, 9 (16), 5881–5888. doi: https://doi.org/10.1002/cam4.3273

10. Society AC. Cancer Facts & Figures (2016). American Cancer society.

11. Chen, X., Yuan, Z., Lu, M., Zhang, Y., Jin, L., Ye, W. (2016). Poor oral health is associated with an increased risk of esophageal squamous cell carcinoma – a population-based case-control study in China. International Journal of Cancer, 140 (3), 626–635. doi: https://doi.org/10.1002/ijc.30484

12. Andrici, J., Eslick, G. D. (2015). Hot Food and Beverage Consumption and the Risk of Esophageal Cancer. American Journal of Preventive Medicine, 49 (6), 952–960. doi: https://doi.org/10.1016/j.amepre.2015.07.023

13. Mathieu, L. N., Kanarek, N. F., Tsai, H.-L., Rudin, C. M., Brock, M. V. (2013). Age and sex differences in the incidence of esophageal adenocarcinoma: results from the Surveillance, Epidemiology, and End Results (SEER) Registry (1973-2008). Diseases of the Esophagus, 27 (8), 757–763. doi: https://doi.org/10.1111/dote.12147

14. Mchembe, M. D., Rambau, P. F., Chalya, P. L., Jaka, H., Koy, M., Mahalu, W. (2013). Endoscopic and clinicopathological patterns of esophageal cancer in Tanzania: experiences from two tertiary health institutions. World Journal of Surgical Oncology, 11 (1). doi: https://doi.org/10.1186/1477-7819-11-257

15. Ferndale, L., Sartorius, B., Aldous, C., Thomson, S. (2019). Oesophageal cancer in Area 2 of Kwazulu-Natal: predictors of late presentation. South African Journal of Surgery, 57(2), 3–9. doi: https://doi.org/10.17159/2078-5151/2019/v57n2a2948

16. Ueda, H., Takeda, M., Ueda, S., Kawakami, H., Okuno, T., Takegawa, N. et al. (2017). Clinical evaluation of palliative chemoradiotherapy for metastatic esophageal cancer. Oncotarget, 8 (46), 80286–80294. doi: https://doi.org/10.18632/oncotarget.17925

17. Wu, S.-X., Li, X.-Y., Xu, H.-Y., Xu, Q.-N., Luo, H.-S., Du, Z.-S. et al. (2017). Effect of consolidation chemotherapy following definitive chemoradiotherapy in patients with esophageal squamous cell cancer. Scientific Reports, 7 (1). doi: https://doi.org/10.1038/s41598-017-17254-9

18. Xia, Y., Li, Y., Chen, Y., Liu, Q., Zhang, J., Deng, J. et al. (2018). A phase II trial of concurrent chemoradiotherapy with weekly paclitaxel and carboplatin in advanced oesophageal carcinoma. International Journal of Clinical Oncology, 23 (3), 458–465. doi: https://doi.org/10.1007/s10147-018-1240-4

19. Ai, D., Zhu, H., Ren, W., Chen, Y., Liu, Q., Deng, J., Ye, J. (2017). Patterns of distant organ metastases in esophageal cancer: a population-based study. Journal of Thoracic Disease, 9 (9), 3023–3030. doi: https://doi.org/10.21037/jtd.2017.08.72

Received date 14.06.2022
Accepted date 24.01.2023
Published date 31.01.2023

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