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RESEARCH ARTICLE

Definitive Chemoradiation with Concurrent Weekly Cisplatin in the Treatment of Esophageal Squamous Cell Carcinoma – A Simplistic Approach

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Abstract

Purpose: Chemoradiation is the standard of care in locally advanced/ inoperable esophageal squamous cell cancer (ESCC). Though combination chemotherapy with Cisplatin and 5-Fluorouracil is the standard, it has low compliance due to toxicities and prolonged treatment time. Hence there is a window of opportunity to explore a safer chemotherapy regimen without compromising the treatment outcome. **Methods:** 55 patients of ESCC who were treated with definitive External Beam Radiotherapy (EBRT) to a dose of 50.4 – 59.4 Gray and concurrent weekly Cisplatin (or Carboplatin) were retrospectively evaluated for treatment efficacy and outcomes. 2 year Overall Survival (OS) and Progression Free Survival (PFS) were evaluated. Prognostic variables were assessed with respect to OS in Univariate analysis. **Results:** Median age at presentation was 58 years. 29 (53%) had lesion in the upper third of esophagus. 40 (72%) had T3 disease and 31 (56%) were node positive. All patients (100%) completed planned radiotherapy dose. 54 (98%) received 4 or more cycles of weekly chemotherapy. Mean overall treatment time was 43 days. Only 7 patients (12.7%) had grade 3 or more acute toxicity. 36 (65.5%) had complete response. At median follow-up of 13.7 months, the median OS was 15.2 months and 2 year OS was 42.6%. On univariate analysis, patients with comorbidities and lower third lesion had poor OS (p=0.016 and p=0.002). Stage II disease and complete response to treatment showed better OS (p=0.02 and p=0.00). **Conclusion:** Radical chemoradiation with weekly Cisplatin in ESCC is a simple and effective regimen which needs to be explored in larger trials.

Keywords: Esophageal squamous cell carcinoma- Chemoradiation- Cisplatin

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Introduction

Concurrent chemoradiation is the treatment of choice in patients with locally advanced/un-resectable Esophageal squamous cell carcinoma (ESCC). With the results of Radiation Therapy Oncology Group (RTOG) 85-01 [1-2] and RTOG 94-05 [3] trials, radical chemoradiation with Cisplatin and 5-Fluorouracil (5-FU) is the standard of care in these patients. The two year overall survival (OS) was 36-40%. But at the same time, grade 3-4 toxicities were high (65-70%), compliance was low (54% patients received all four cycles of chemotherapy) and the overall treatment time was long (100 days).

Use of weekly Cisplatin as radiosensitizer is a very modest way of incorporating concurrent chemotherapy in radical treatment of squamous cell carcinoma of cervix [4-5] and head and neck [6] cancers. Because of the ease of administration and better treatment compliance, radical chemoradiation with weekly cisplatin has been routinely used to treat ESCC in our Institution. Hence, we evaluated the efficacy and treatment outcomes of concurrent chemoradiation with weekly Cisplatin in patients of locally advanced ESCC. Preliminary data of 20 patients was presented as abstract in World GI congress in 2017 [7].

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Materials and Methods

From April 2015 to December 2019, out of 108 esophageal squamous cell carcinoma (ESCC) patients seen by a single radiation oncologist, 94 were treated with radical intent. Of these 94 patients, 55 were treated with weekly Cisplatin and Radiotherapy (RT). These 55 ESCC patients were retrospectively analyzed with respect to efficacy and treatment outcomes.

All 55 patients had Karnofsky Performance Status (KPS) of 70 and above. All patients underwent baseline Upper Gastro Intestinal (UGI) endoscopy and Contrast Enhanced Computed Tomography (CECT) of thorax and upper abdomen or Whole Body Positron Emission Tomography (WB-PET) for loco-regional evaluation and to rule out distant metastasis. All patients were staged with TNM 6th edition staging [8]. Patients with near complete dysphagia had undergone feeding jejunostomy (FJ) before start of treatment.

Radiotherapy

All patients were immobilized in supine position with 4 clamp thoracic thermoplastic mask followed by CECT simulation with or without oral contrast. Gross Tumor Volume (GTV) included the primary tumor and the enlarged nodes defined based on the CECT and UGI endoscopy findings. Clinical Target Volume (CTV) was defined as GTV plus 4 cm cranio-caudal and 1 cm radial margin. A 5 mm Planning Target Volume (PTV) expansion was given to this CTV to be treated to a dose of 45 Gray (Gy) in 25 fractions over 5 weeks in phase 1. In Phase 2, GTV with 1.5 cm cranio-caudal and 5 mm radial margin constituted the CTV to which 5 mm PTV expansion was given which was boosted to a dose of 5.4-14.4 Gy in 3-8 fractions. Organs at Risk (OAR) - Lungs, Cardia and spinal cord were contoured. Treatment planning was done with Eclipse version 11 treatment planning system using 4 field 3 Dimensional Conformal Therapy (3DCRT) or 7 fields Intensity Modulated Radiotherapy (IMRT) technique.

Chemotherapy

Chemotherapy consisted of intravenous Cisplatin administered at a dose of 40 mg/m^2 every week concurrent with radiation. Weekly Carboplatin at a dose of Area under Curve (AUC) – 2 was also given weekly in patients with deranged Renal Function Test (RFT). Baseline and weekly Complete blood Count (CBC), RFT were done at start of each chemotherapy cycle.

Toxicity Evaluation and Response Assessment

Acute toxicities during the course of chemoradiation were assessed according to RTOG-EORTC acute radiation toxicity grading [9]. Weight loss, hospital admission for any supportive care and treatment interruption were documented.

Response assessment was done with UGI endoscopy and CECT thorax and abdomen/WBPET-CT at 3 months post treatment and assessed according to RECIST criteria [10].

Statistics

Data was collected retrospectively and the results were analyzed using SPSS version 16. Overall survival (OS) was defined as the time between the dates of start of treatment to the date of death/last seen in clinic/ last telephonic information. Progression Free Survival (PFS) was defined as the dates of start of treatment to the date of progression of disease as assessed by UGI endoscopy or CECT. Kaplan-Meier estimates were performed to calculate the OS and PFS. Univariate analysis with log rank test was performed to study different factors correlating to survival and a p value < 0.05 was considered statistically significant. The factors found to have statistically significant association with survival were further analyzed in multivariate analysis using cox regression model.

Results

Patient and treatment characteristics

Median age at presentation was 58 years (range 28-82), 32 (58%) were male. 17 (31%) had co-morbidities, 27 (49%) had history of addiction to alcohol or tobacco. Lesion was situated in upper third in 29 (53%). 40 (72%) had T3 disease and 31 (56%) were node positive. Mean length of primary tumor was 6.2 cm; more than half of the patients (56%) had stricture. 44 (80%) patients were treated with 3DCRT technique and 20% with IMRT. All patients (100%) completed planned RT. 17 (31%) received more than 50Gy (56 Gy and 59.4 Gy dose protocol). 43 (73%) received Cisplatin chemotherapy. Median chemotherapy cycles were 5. 54 patients (98%) received 4 or more cycles. The mean overall treatment time (OTT) was 43 days. Details are summarized in Table 1.

Acute toxicities

Only 7 patients (12.7%) had grade 3 acute hematological toxicities none of these were seen in patients who received carboplatin. All were self-limiting not requiring any intervention. Mean weight loss was 4.2 kg (7% of baseline weight) 3 patients gained weight. No treatment related deaths were reported. Acute toxicities are shown in Table 2.

Treatment response and failure patterns

Response assessed at 3 months showed complete response (CR) in 36 patients (65.5%), 14 (25.4%) had partial response (PR), 5 (9%) had progressive disease (PD). 2 out of 14 PR patients received palliative chemotherapy and both are alive with disease; remaining 12 patients denied any further intervention. None of them were considered for salvage surgery due to poor performance status. 4 of the 5 PD patients had local and distal progression and 1 patient had loco-regional progression. All of these patients received palliative chemotherapy and eventually succumbed to disease.

Of the 36 patients who had CR, 8 patients recurred. 2 had local only, 3 had loco-regional, 1 had regional, 1 had isolated distal and 1 had local and distal failure. 4 of these patients received palliative chemotherapy.

Table 1. Patient and Disease Characteristics

Characteristics	Number (Total 55)	Percentage (%)
Age (years)		
Median	58 (28 – 82)	
<60 vs >60	28 vs 27	50.9 vs 49.1
Sex		
Male : Female	32:23	58.2 : 41.8
Comorbidities		
Yes / No	17 / 38	30.9 / 69.1
Addiction		
Yes / No	27 / 28	49.1 / 50.9
Histology Grade		
G1 / G2	6/35	10.9 / 63.6
G3 / NOS	2/12	3.6 / 21.8
Site of Tumor		
Upper	29	52.7
Middle	14	25.5
Lower	12	21.8
T Stage		
T2	14	25.5
T3	40	72.7
T4	1	1.8
N Stage		
N0 : N1	24:31	43.6 : 56.4
Stage Group		
IIA / IIB	28 / 7	50.9 / 12.7
III	20	36.3
Length (cm)		
Mean	6.2 (2 – 14)	
Tumor Diameter (cm)		
Mean	4.3 (2.7 – 6.3)	
Tumor Volume (cc)		
Mean	47.1 (10.1 – 131)	
Stricture		
Yes / No	31 / 24	56.4 / 43.6
Feeding Procedure		
Yes / No	17 / 38	30.9 / 69.1
Hemoglobin Baseline (gm/dl)		
Mean	12.6 (6.8 – 17.8)	
Albumin Baseline (gm/dl)		
Mean	3.6 (2.8 – 5)	
Radiation Dose (Gray)		
Mean	50.4 (50 – 60)	
Chemotherapy Agent		
Cisplatin	43	78.2
Carboplatin	12	21.8
Chemotherapy Cycles		
Median	5 (3 – 6)	
Overall Treatment Time (Days)		
Median	43 (36 – 53)	

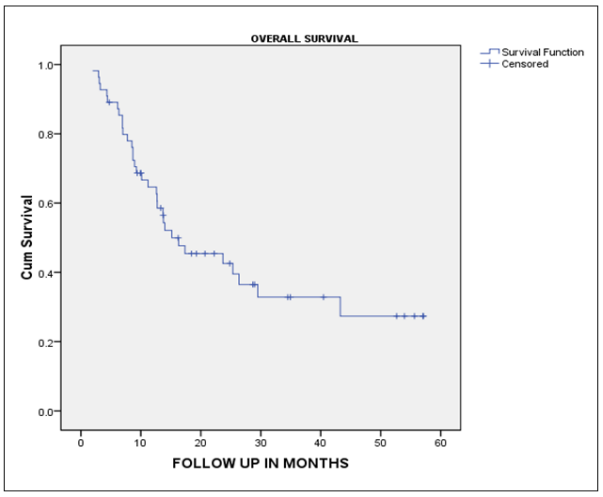

Figure 1. Overall Survival

Overall survival and Progression free survival

Median follow-up was 13.7 months (range 3-57 months); median follow up in patients who are alive was 23.5 months. The median OS was 15.2 months. 1 year, 2 year OS was 63.8% and 42.6% respectively. Median PFS was 11.6 months. Survival curves for OS and PFS are shown in Figures 1 and 2.

Univariate and Multivariate analysis

On Univariate analysis, presence of comorbidities and lower third location of primary lesion showed poor OS (p = 0.01 and 0.00) and PFS (p = 0.01 and p = 0.01). Stage II disease and CR to treatment showed better OS (p = 0.02 and 0.00) and PFS (p = 0.02 and p = 0.00). Node negative disease showed better PFS (p = 0.03) and trend towards better OS (P = 0.05). Length of primary lesion (<5cm vs. >5cm), RT dose of more than 50.4 Gy, RT technique (3DCRT vs. IMRT) or type of chemotherapy agent (Cisplatin vs. Carboplatin) did not show any statistically significant difference with respect to OS and PFS. Complete Univariate analysis of the potential prognostic variables is shown in Table 3.

Those prognostic factors with significant p value on Univariate analysis, which is presence of comorbidities, Stage II disease, lower third location of tumor, node negative disease and CR to treatment, were further evaluated with Cox regression multivariate analysis. Only comorbidities and CR to treatment were found to be statistically significant for OS (p = 0.046 and p = 0.00), whereas only CR to treatment was found to be statistically significant for PFS (p = 0.00).

Discussion

The median OS in our study was 15.2 months and 2 year OS was 42.6%, which are similar to the results of RTOG studies [1, 3] where the median OS was 12.5 months, 18 months and 2 year OS was 38%, 40% respectively. The chemoradiation arm of FFCD 9102 [11] and Cisplatin-5 FU arm of Prodige5/Accord17 [12] trials also show similar OS rates (2 year OS 39.8% and 3 year

Table 2. Acute Toxicities

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3
Anaemia	32 (58.2%)	15 (27.3%)	7 (12.7%)	1 (1.8%)
Leucopoenia	20 (36.4%)	13 (23.6%)	16 (29.1%)	6 (10.9%)
Neutropenia	35 (63.6%)	7 (12.7%)	8 (14.5%)	5 (9.1%)
Thrombocytopenia	51 (92.8%)	2 (3.6%)	1 (1.8%)	1 (1.8%)
Overall Grade 3		7 (12.7%)		

OS 26.9 respectively). CR rates in our study was 65.5% better than the rates reported in Prodige5/Accord17 [12] and JCOG 9906 [13] trials (62% and 43% respectively).

Grade 3 and more acute toxicities in our study were 12.7% (7/55) and all of these were hematological and were self-limiting not requiring any intervention. No treatment related deaths were reported. Whereas, in the RTOG trials [1, 3] overall grade 3 or more acute toxicities were 66% and 71% respectively. Grade 3 or more hematological toxicities in RTOG [1, 3] ,FFCD 9102 [11] , JCOG 9906 [13], Prodige5/Accord17 [12] and ESO Shanghai 1 [14] trials were – 48%, 22%, 43%, 44% and 19% respectively, probably attributable to the over lapping toxicity of combination drug regimen of Cisplatin and 5-FU given in systemic doses. Also these studies showed different spectrum of toxicities like oral mucositis, pharyngitis which are outside radiotherapy treatment fields mainly attributable to 5-FU. Trials using newer chemotherapeutic drugs like Paclitaxel [14] or different combination of chemotherapeutic agents like FOLFOX [12] neither have improved outcomes nor curtailed the toxicities.

In all these studies per protocol overall treatment time was (OTT) was 95 – 110 days (including 2 cycles of adjuvant chemotherapy). Inpatient treatment was required for continuous infusion chemotherapy regimen. Whereas mean OTT in our study was 43 days (less than half of the OTT compared to these studies) and chemotherapy was administered on daycare basis. In RTOG 85-01 [1], out of 61 patients in chemoradiation arm, 10 patients expired within this treatment time of 100 days who could not be assessed. When the median PFS is 9-12 months, one-third of this time being spent in treatment itself has to be weighed against the benefits.

In our study all patients (100%) completed planned RT without significant treatment breaks and 70% received at least 5 cycles of cisplatin. Our study patients did not receive any planned adjuvant chemotherapy. In RTOG trials [1, 3] only 54% and 40.3% received all 4 planned chemotherapy cycles. It is also seen that the results of trials published after 2005 have good compliance where 70% received all 4 cycles. It also means 30-50% did not receive planned adjuvant chemotherapy which was an integral part of treatment. As per the Patterns of failure in all of these studies and our study too, loco-regional failure still accounts for more than half of all the recurrences. Even if distal recurrence occurs isolated distal metastasis is a rarity. Our Univariate analysis showed a strong relation of CR rates and OS (p value = 0.00). A concurrent chemoradiation regimen able to achieve better CR rates should be able to translate to a better OS. Hence the role of adjuvant chemotherapy in locally advanced ESCC treated with concurrent chemoradiation might be of questionable benefit.

JCOG 9906 [13] and ESO Shanghai 1 [14] trial have shown better treatment compliance and better OS outcomes over and above the historical results of RTOG 8501 [1]. Authors were perplexed by the results [14] and attributed this to be probably due to Asian ethnicity of the patients and good supportive care. Also patients in these studies received escalated RT dose of 60 – 61.4 Gy at 1.8-2 Gy/ fractions (delivered with conformal therapy in ESO shanghai 1 trial). Though 31% in our study received more than 50 Gy, on Univariate analysis increased dose did not show statistically significant association to OS, though number was less. A small percentage of patients also underwent salvage surgery in the JCOG 9906 trial [13]. It is seen that 6-34% undergo salvage surgery after chemoradiation and among them some have OS benefit (5 year OS 25-35%), albeit high rates of hospital deaths (6-33%) [15-17]. None of the patients who had PR in our study underwent salvage surgery, as many of these patients were sent for radiotherapy since they were deemed surgically unfit due to upper third disease or being frail.

Studies comparing concurrent chemoradiation with single agent versus multi agent chemotherapy have also suggested that single-agent chemoradiation are not inferior to multi-agent treatment in terms of outcomes, and are better tolerated with good toxicity profiles [18-19]. Again these are retrospective, institutional experiences.

Our study is comparable to the historical standards as well as recent trials in terms of outcome. With respect to the toxicity profile, OTT, treatment compliance and

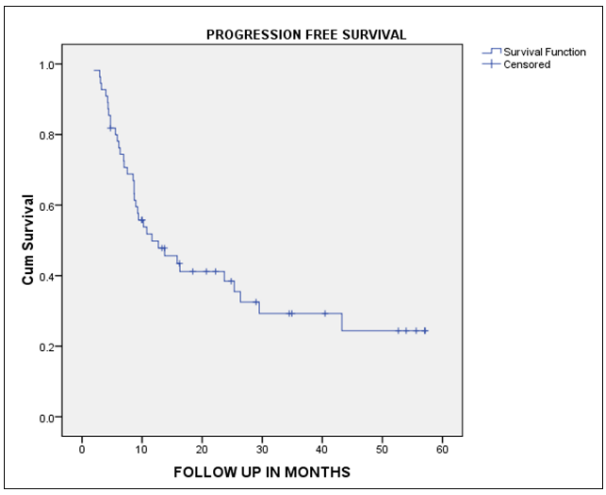

Figure 2. Progression Free Survival

Table 3. Univariate Analysis of Prognostic Factors Affecting the Overall Survival (OS) and Progression Free Survival (PFS)

Prognostic Variables	Median OS (months)	P value (<0.05)	Median PFS (months)	P value (<0.05)
Age (years)				
<60 vs >60	16.3 vs 14.0	0.92	11.6 vs 12.7	0.97
Sex				
Male Vs Female	14.0 vs 23.7	0.3	10.8 vs 23.7	0.16
Comorbid				
Yes vs No	11.2 vs 23.7	0.01	8.5 vs 16.3	0.01
Addiction				
Yes vs No	25.3 vs 13.7	0.38	15.8 vs 10.2	0.71
Histology Grade				
G1 / G2 / G3	13.7 vs 12.7 vs 11.2	0.19	13.7 vs 9.2 vs 8.5	0.08
Site of Tumor				
Upper/ Middle/ Lower	25.3 vs 26.3 vs 7.7	0	15.8 vs 13.7 vs 6.1	0.01
T Stage				
T2 vs T3/T4	25.3 vs 13.7	0.28	15.8 vs 10.2	0.66
N Stage				
N0 vs N1	29.5 vs 12.7	0.05	25.3 vs 9.4	0.03
Stage Group				
II vs III	29.5 vs 12.6	0.02	16.3 vs 9.2	0.02
Length (cm)				
<5 vs >5	25.3 vs 13.7	0.37	25.3 vs 10.2	0.37
Tumor Diameter (cm)				
<4 vs >4	25.3 vs 13.7	0.29	15.8 vs 10.8	0.87
Tumor Volume (cc)				
<40 vs >40	25.3 vs 13.7	0.21	15.8 vs 10.8	0.66
Stricture				
Yes vs No	13.7 vs 25.3	0.19	9.2 vs 12.7	0.48
Feeding Procedure				
YES vs NO	13.7 vs 17.3	0.23	9.2 vs 12.7	0.51
Hemoglobin Baseline (gm/Dl)				
<12/>12	10.1 vs 16.3	0.37	8.6 vs 12.7	0.4
Albumin Baseline (gm/dl)				
<4 vs >4	13.7 vs 15.1	0.92	11.6 vs 13.7	0.98
Radiation Technique				
3DCRT vs IMRT	16.3 vs 14.0	0.55	10.2 vs 26.3	0.33
Radiation Dose (Gray)				
50 vs >50	13.7 vs 26.3	0.13	9.4 vs 26.3	0.17
Chemotherapy Agent				
Cisplatin Vs Carboplatin	15.2 vs 16.3	0.62	13.7 vs 11.6	0.24
Chemotherapy Cycles				
<4 vs >4	11.2 vs 23.7	0.15	10.2 vs 16.3	0.12
Overall Treatment Time (Days)				
<42 vs >42	13.7 vs 16.3	0.41	8.9 vs 16.3	0.12
Treatment Response				
Complete vs others	29.5 vs 8.5	0.00	26.3 vs 6.3	0.00

Table 4. Comparison of Present Study with Chemoradiation Studies

	No. of Patients	Median OS (months)	2 Year OS	Chemo Agent	Grade 3/> Acute Toxicity	Compliance [a]	OTT [b] (Days)
Present Study	55	15.2	42.60%	Weekly Cisplatin (CONC)	12.7% (H)	69%	43
RTOG 8501 (Herskovic 1992)	61/121	12.5	38%	3 Weekly Cisplatin+5-FU (CONC+ADJ)	66% (OA) 48% (H)	54%	100
RTOG 9405 (Minsky 2002)	109/218	18	40%	4 Weekly Cisplatin+5-FU (CONC+ADJ)	71% (OA) 2 Deaths	40.3% [c]	100
FFCD 9102 (Bedenne 2007)	130/259	19.3	39.80%	3 Weekly Cisplatin+5-FU (CONC+ADJ)	31% (OA) 22% (H)	97% [d,e]	97
JCOG 9906 (Kato 2011)	76	28	44.70% (3yr)	Weekly Cisplatin+5-FU (CONC+ADJ)	43% (H)	70% [d]	110
Prodige5/ACCORD17 (Conroy 2014)	133/267	17.5	26.50% (3yr)	3 Weekly Cisplatin+5-FU (CONC+ADJ)	44% (H) 6 DEATHS	76%	95
ESO Shanghai1 (Chen 2019)	219/436	40	61%	4 Weekly Cisplatin+5FU (CONC+ADJ)	51% (OA) 19% (H)	69%	110

H – hematological, OA – overall, OS – overall survival, OTT – overall treatment time; • a - All 4 cycles (including adjuvant chemotherapy); • b - Including adjuvant chemotherapy; • c - Data available for 59% patients among them (44 patients) received per protocol chemo; • d - 2 weeks planned treatment gap during RT; • e - compliance rate calculated at randomization before 2nd phase of continuation RT; CONC, Concurrent; ADJ, Adjuvant

ease of administration of concurrent chemotherapy, our study reasonably scores better than these studies. Data shown in Table 4 compares present study with the published studies. But at the same time ours is a single institution retrospective data, which is the drawback. But most of the data were well maintained longitudinally. Outcomes can be further enhanced if RT doses can be safely escalated with the modern conformal treatment and judicious use of salvage surgery in well selected patients.

In conclusion, concurrent chemoradiation with weekly Cisplatin in ESCC is simple and effective regimen which needs to be evaluated in a larger prospective study.

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