

## RESEARCH ARTICLE

# Weekly Cisplatin-Based Concurrent Chemoradiotherapy for Treatment of Locally Advanced Head and Neck Cancer: a Single Institution Study

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## Abstract

**Background:** The organ preservation approach of choice for the treatment of locally advanced head and neck cancers is concurrent chemoradiation with three weekly high doses of cisplatin. Although this is an efficacious treatment policy, it has high acute systemic and mucosal toxicities, which lead to frequent treatment breaks and increased overall treatment time. Hence, the current study was undertaken to evaluate the efficacy of concurrent chemoradiation using 40 mg/m<sup>2</sup> weekly cisplatin. **Materials and Methods:** This is a single institutional retrospective study including the data of 266 locally advanced head and neck cancer patients who were treated with concurrent chemoradiation using 40 mg/m<sup>2</sup> weekly cisplatin from January 2012 to January 2014. A p-value of <0.05 was taken to be significant statistically for all purposes in the study. **Results:** The mean age of the study patients was 48.8 years. Some 36.1% of the patients had oral cavity primary tumors. The mean overall treatment time was 57.2 days. With a mean follow up of 15.2 months for all study patients and 17.5 months for survivors, 3 year local control, locoregional control and disease free survival were seen in 62.8%, 42.8% and 42.1% of the study patients. Primary tumor site, nodal stage of disease, AJCC stage of the disease and number of cycles of weekly cisplatin demonstrated statistically significant correlations with 3 year local control, locoregional control and disease free survival. **Conclusions:** Concurrent chemoradiotherapy with moderate dose weekly cisplatin is an efficacious treatment regime for locally advanced head and neck cancers with tolerable toxicity which can be used in developing countries with limited resources.

**Keywords:** Head and neck cancer - organ preservation treatment - chemoradiation - cisplatin dosage

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## Introduction

Some 57.5% of the worldwide head and neck cancers (excluding oesophageal cancers) occur in Asia, especially in India (Chaturvedi, 2009). The reported burden of head and neck cancers (HNCA) in India is actually much less and is analogous to the tip of the iceberg (Mishra et al., 2014). Most of the patients with HNCA present in Stage IV disease in India (Pandey et al., 2014).

Chemoradiotherapy based organ preservation approach is currently the standard of care for the management of HNCA (Lasrado et al., 2014). According to the meta-analysis of the MACH-NC collaborative group (Pignon et al., 2007), which demonstrated a 6.5% absolute survival advantage at 5 years in HNCA with concurrent chemoradiation, platinum based concurrent chemoradiation has become the non-surgical standard of care in the treatment of locally advanced head and neck cancers (LAHNC). Although 3 weekly high dose

cisplatin is the current chemotherapy of choice while given concurrently with radiation (Pignon et al., 2000; Pignon et al., 2005; Pignon et al., 2007), there is still no uniform consensus due to the wide variation in various study designs and due to the different ways of combining chemotherapy with radiation (Browman et al., 2001; Baykara et al., 2013). Also the 3 weekly high dose cisplatin based chemoradiation regime has been shown to have considerable mucosal and haematological toxicity and is non-compliant in one-third of the patients (Brizel et al., 2006). The situation is further complex in developing countries like India, where there are limited resources and the patients need intensive inpatient care for the acute toxicities. Hence, moderate doses of weekly cisplatin has been advocated as concurrent chemotherapy (Dimri et al., 2013) while the patient is on radiation.

The current study aims at finding out the efficacy of moderate dose weekly cisplatin based concurrent chemoradiation in Indian setting.

## Materials and Methods

### Study design

This is a single institutional retrospective study done with the data available from the computer and clinical case sheets of the patients with locally advanced squamous cell carcinoma of the head and neck who were treated in the Department of Radiotherapy in a South Indian institute from January 2012 to January 2014. Previously untreated patients with non-metastatic LAHNC (excluding cancers of the esophagus, nasopharynx and paranasal sinuses) who were treated with 40 mg/m<sup>2</sup> cisplatin based concurrent chemoradiation were only included in the study. Patients treated with neoadjuvant or adjuvant chemotherapy were excluded from the study. Patients treated with any other chemotherapeutic agents or with any other dosage regime of cisplatin were also excluded from the study. All patients who completed their treatment were only included in the present study. A total of 266 patients were found to be satisfying the inclusion criteria of the study.

### Radiotherapy

All patients were treated with conventional radiotherapy with 6 MV photons with a linear accelerator after immobilization with thermoplastic mask. All patients were treated with conventional fractionation. The gross tumor volume was treated to a dose of 66 or 70 Gy in 33 - 35 fractions. The first phase 46 Gy was delivered in 23 fractions to the mid-plane with pair opposing lateral fields. The lower neck was treated with a matched low anterior neck field upto a dose of 50 Gy in 25 fractions using a half beam block, normalized at 2-3 cms of depth. In the second phase, shrinking field off-cord technique was used to deliver the radiation dose to the primary tumor site along with the nodal sites with a 2-3 cms margin upto a dose of 66 or 70 Gy.

### Chemotherapy

40 mg/m<sup>2</sup> weekly cisplatin was administered intravenously during the course of radiation. Pre-chemotherapy hydration was given along with standard antiemetic premedication. Cisplatin was delivered along with 500 ml of normal saline over 3 hours. Post-chemotherapy hydration was given along with 10 ml of magnesium sulphate. 100 ml of 20% mannitol was given post-chemotherapy to ensure forced diuresis. On the day of the chemotherapy, radiation was delivered within an hour of cisplatin administration. Post-chemotherapy antiemetic prophylaxis was given. Chemotherapy administration was postponed if the haemoglobin level was less than 9 gm/dl or total leukocyte count was less than 2500 mm<sup>-3</sup> or platelet count was less than 75,000 mm<sup>-3</sup> or serum creatinine was more than 1.5 mg%, till recovery. Dose modifications were not done in any patient.

### Patient evaluation

All the study patients were evaluated weekly during the course of chemoradiotherapy to assess the toxicity of the treatment. After completion of chemoradiation, all patients were followed up monthly for the next two months, then every 3-6 monthly for the next 2 years and

annually thereafter. All acute toxicities were recorded according to the Radiation Therapy Oncology Group (RTOG) guidelines (Cox et al., 1995). Disease control was assessed clinically and with direct laryngoscopy whenever indicated. Patients who did not turn for follow up were considered lost to follow up and were censored for statistical analysis.

### Statistical analysis

Local failure was defined as persistence or reappearance of disease at or in close proximity to the primary tumor site. Locoregional failure was defined as persistence or reappearance of the disease either at the primary site or in draining regional lymph nodes. Relapse was defined as recurrence of disease at either the primary, regional or distant site or the appearance of a second primary in the upper aero-digestive tract. All data were tabulated in Microsoft Excel and analysed with SPSS (Statistical Package for Social Sciences) software version 20. The local control, loco-regional control and disease free survival were calculated using the Kaplan-Meier method. All the estimates were calculated from the date of initiation of treatment till the defined event if any or until last contact or death. The analysis was limited only to first failures as a measure of efficacy of concurrent chemoradiotherapy and does not include the outcome after attempted salvage treatments. The data was compared using the Log-rank test for univariate analysis. p -value < 0.05 was taken to be statistically significant.

## Results

The mean age of the study patients was 48.8 years. 59% of the study patients were of age less than equal to 50 years. 36.1% of the study patients had primary oral cavity tumors, mostly of the hard palate and buccal mucosa. 31.2%, 17.3% and 15.4% patients had primary tumors in the oropharynx, hypopharynx and larynx respectively. 53.8% patients had T3 tumors. Majority of the patients had N2 disease. 54.5% of the study patients had AJCC Stage IV tumors at diagnosis. 65.4% of the patients received 66 Gy dose of radiation, while rest of the study patients received 70 Gy. Majority of the study patients (78.2%) received more than 4 cycles of weekly cisplatin (Table 1). The mean overall treatment time of the study patients was 57.2 days. 54.5% patients completed their treatment within 57 days (Table 1).

### Local control

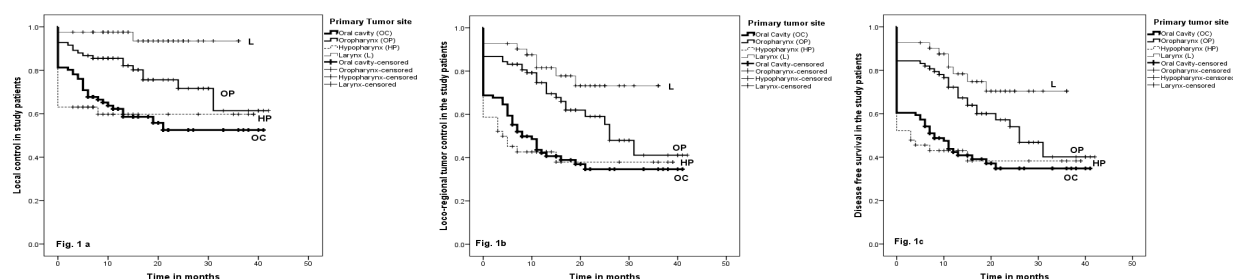
With a mean follow up of 15.2 months for all study patients and 17.5 months for survivors, the 3 year local control was 62.8%. Primary tumor site (<0.001) (Figure 1a), T stage (<0.001), nodal stage (<0.001), AJCC tumor stage (0.014) (Figure 2a), cycles of concurrent weekly cisplatin (<0.001) and overall treatment time (0.009) showed statistically significant association with local tumor control in the study patients (Table 1).

### Locoregional control

The 3 year locoregional control of the study patients was 42.8%. Primary tumor site (<0.001) (Figure 1b), N

**Table 1. Univariate Analysis of the Prognostic Factors for 3 Year Local Control, Loco-Regional Control and Overall Control in the Study Patients**

Prognostic Factor	Number of Patients (%)	3 year Local Control %	p- value	3 year Locoregional Control %	p- value	3 year Overall Control %	p- value
<b>Age</b>							
≤ 50 years	157 (59%)	63.60%	0.677	41.00%	0.246	40.50%	0.342
> 50 years	109 (41%)	62.90%		46.90%		46.00%	
<b>Primary tumor site</b>							
Oral cavity	96 (36.1%)	52.50%	<0.001	34.60%	<0.001	34.80%	<0.001
Oropharynx	83 (31.2%)	61.40%		41.10%		40.10%	
Hypopharynx	46 (17.3%)	59.70%		37.90%		38.20%	
Larynx	41 (15.4%)	93.50%		73.20%		70.40%	
<b>T Stage</b>							
T 1	20 (7.5%)	100%	<0.001	27.70%	0.052	25.70%	0.088
T 2	60 (22.6%)	69%		38.00%		39.20%	
T 3	143 (53.8%)	63.30%		47.90%		46.90%	
T 4	43 (16.2%)	41.60%		39.40%		39.60%	
<b>N Stage</b>							
N 0	51 (19.2%)	67.20%	<0.001	57.30%	<0.001	57.30%	<0.001
N 1	86 (32.3%)	65.70%		47.40%		46.90%	
N 2	103 (38.7%)	67.60%		38.20%		36.80%	
N 3	26 (9.8%)	33.90%		11.50%		11.50%	
<b>AJCC Stage</b>							
Stage III	121 (45.5%)	66.70%	0.014	49.80%	0.018	49.50%	0.016
Stage IV	145 (54.5%)	61.90%		36.80%		35.80%	
<b>RT Dose</b>							
66 Gy	174 (65.4%)	56.90%	0.705	35.20%	0.085	34.30%	0.054
70 Gy	92 (34.6%)	70.50%		56.70%		56.80%	
<b>Cycles of Chemotherapy</b>							
≤ 4	58 (21.8%)	42.70%	<0.001	21.10%	<0.001	18.50%	<0.001
> 4	208 (78.2%)	68.40%		49.60%		49.10%	
<b>Overall treatment time</b>							
≤ 57 days	145 (54.5%)	72.70%	0.009	50.00%	0.05	48.40%	0.089
> 57 days	121 (45.5%)	45.30%		29.90%		30.10%	

**Figure 1. Primary Tumor Site as a Prognostic Factor for Local Control (1a), Loco-regional Control (1b) and Disease Free Survival (1c) in LAHNC Treated with Moderate dose weekly Cisplatin Based Concurrent Chemoradiotherapy**

stage (<0.001), AJCC tumor stage (0.018) (Figure 2b) and number of cycles of chemotherapy (<0.001) demonstrated significant statistical correlation with the locoregional tumor control (Table 1). Overall treatment time showed an almost significant statistical association (p-value 0.05) with locoregional control of tumor (Table 1).

#### Disease free survival

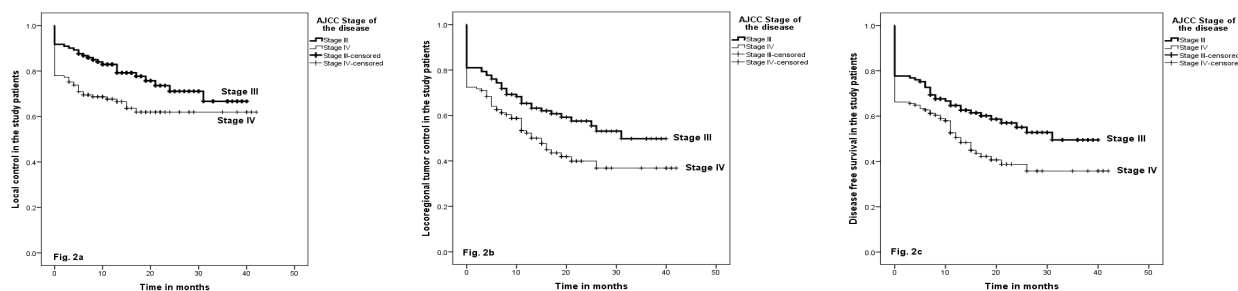
The 3 year disease free survival of the study patients was 42.1%. Primary tumor site (<0.001) (Figure 1c), N stage (<0.001), AJCC tumor stage (0.016) (Figure 2c) and number of cycles of chemotherapy (<0.001) demonstrated significant statistical correlation with the disease free survival (Table 1).

#### Acute toxicity

Radiation Therapy Oncology Group (RTOG) Grade III or IV acute toxicities like mucositis, dermatitis, emesis, and haematological toxicity were seen in 48.1%, 36.8%, 7.1%, and 7.9% of the patients respectively.

#### Treatment breaks

This study gives a true picture of rural India, where inadvertent treatment breaks are created in 34.2% (91) of the study patients due to the lack of knowledge and reluctance of the patients and their attenders, thereby prolonging the overall treatment time. 27.4% of the study patients experienced treatment breaks due to acute toxicities.



**Figure 2. AJCC Tumor Stage as a Prognostic Factor for Local Control (2a), Loco-regional Control (2b) and Disease Free Survival (2c) in LAHNC Treated with Moderate Dose Weekly Cisplatin Based Concurrent Chemoradiotherapy**

## Discussion

The present study reports one of the largest single-institutional experience of concurrent weekly cisplatin based chemoradiation in the non-surgical management of LAHNC in South India. The mean age of presentation with LAHNC in our study was 48.8 years. This is quite low when compared to western literature (Fan et al., 2012). But similar mean age of presentation has been reported in Indian studies (Gupta et al., 2009; Dimri et al., 2013). The earlier age of presentation in the current study may be attributed to the habit of tobacco chewing, smoking and also reverse smoking. The most commonly encountered primary tumors were that of oral cavity (hard palate mostly), which can be again attributed to the practice of reverse smoking in this part of the country and also the habit of chewing tobacco and betelnut. The mean overall treatment time was higher in the current study when compared to other literature, because most of the present study patients were illiterate and came from rural background, hence were at times reluctant to come for treatment even after repeated counselling.

A meta-analysis (Pignon et al., 2009) of 87 trials demonstrated a 4.5% absolute benefit of chemotherapy at 5 years. Also, both direct and indirect comparisons demonstrated a more pronounced benefit with concurrent chemotherapy when compared to induction chemotherapy. The absolute benefit was 6.5% at 5 years. Cisplatin acts synergistically with radiation in the treatment of LAHNC in the following ways - as a radiosensitizer by inhibiting potentially lethal and sublethal damage repair, as a hypoxic cell sensitizer, as a cell cycle inhibitor, by forming deoxyribonucleic acid adducts and as an inhibitor of angiogenesis (Marcu et al., 2003). The use of 3 weekly cisplatin at 100 mg/m<sup>2</sup> concurrently with radiation is now recommended in the non-surgical management of LAHNC for organ preservation (Adelstein et al., 2003; Forastiere et al., 2003; Pignon et al., 2007). But only 60% of the patients actually remain fit enough to receive the desired 3 cycles of chemotherapy due to higher systemic and mucosal toxicities (Brizel et al., 2006). The non-compliance is even more in developing countries due to the limited resources (Dimri et al., 2013). Few studies have demonstrated moderate efficacy of weekly 40 mg/m<sup>2</sup> cisplatin based chemoradiotherapy with less toxicity and better patient compliance, especially in developing countries with limited resources (Gupta et al., 2009; Dimri et al., 2013).

In the present study, the 3 year local control, locoregional control and disease free survival was seen in 62.8%, 42.8% and 42.1% of the study patients. Gupta et al. (2009) found a 5 year local control, locoregional control, and disease free survival of 57%, 46%, and 43% respectively. Another study (Dimri et al., 2013), found a 5 year disease free survival of 39.4%. As most of the disease recurrences and relapses in LAHNC occur within the first three years of treatment, the result of the current study is quite in concordance with the other studies from India.

Alike an Indian institutional experience (Gupta et al., 2009), the present study also demonstrated a significant association of local tumor control with primary tumor site, T stage, AJCC stage of the disease, number of cycles of chemotherapy and overall treatment time. Also in the present study, the nodal stage of the disease, AJCC Stage of the tumor, primary tumor site and number of cycles of chemotherapy administered concurrently with radiation demonstrated significant correlation with locoregional tumor control and disease free survival, similar to a study from Mumbai (Gupta et al., 2009).

In the laryngeal preservation trial by Forastiere et al. (Forastiere et al., 2003), only 70% patients received the desired 3 cycles of high dose cisplatin during radiation. Also Grade III or IV pharyngitis, haematological toxicity, emesis and nephrotoxicity were seen in 78%, 47%, 20% and 4% of the study patients respectively. Whereas, a study (Dimri et al., 2013) from India with weekly 35 mg/m<sup>2</sup> cisplatin based chemoradiation demonstrated acute Grade III or IV mucositis, emesis, anemia and leukopenia in 67%, 3%, 0.5% and 0.5% patients respectively. Another study (Gupta et al., 2009) demonstrated acute Grade III or IV mucositis and dermatitis in only 29% and 35% of the study patients respectively. Similarly, in the present study acute Grade III or IV mucositis, dermatitis, emesis and haematological toxicities were seen in 48.1%, 36.8%, 7.1%, and 7.9% of the study patients respectively. Even though most of the patients were from rural background and lacked proper nutrition, the high grade toxicities were quite comparable to other regional studies. Another study (Geeta et al., 2006) with 40 mg/m<sup>2</sup> cisplatin based chemoradiotherapy demonstrated an overall treatment compliance of 65%, significant hematologic toxicity of around 20% and treatment related hospital admissions of approximately 30%.

In conclusion, the treatment of LAHNC with 40 mg/m<sup>2</sup> weekly cisplatin based chemoradiation is an effective and



less toxic regime. It can be especially used in developing nations with limited resources, where intensive in-patient care throughout the period of chemoradiation is hardly possible. The patient compliance improves with this treatment regime, thereby decreasing the treatment breaks and improving local tumor control. The primary site of tumor, AJCC stage of disease and number of cycles of concurrent chemotherapy are important prognostic factors for improved disease free survival in patients with LAHNC. Overall treatment time is an important prognostic factor for the local tumor control in LAHNC.

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