Section: Radiation Oncology

Original Research Article

CONCOMITANT BOOST IRRADIATION WITH WEEKLY LOW-DOSE CHEMOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK CANCERS

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Abstract

Background: Head and neck cancers in India continue to be a major public health problem due to high exposure to smoking. Smoking tobacco among Indian people causes significant morbidity and mortality. **Aim**: This study aimed to evaluate the use of altered fractionation as a Concomitant boost and low-dose chemotherapy in the form of weekly CDDP and Paclitaxel. **Materials and Methods:** This single-arm prospective study was conducted between January 2015 and August 2015 in the Department of Radiotherapy, Barnard Institute of Radiology & Oncology, Madras Medical College, Chennai. Thirty consecutive patients with histopathologically proven squamous cell carcinoma of the head and neck who were fit for inclusion criteria were recruited from the outpatient department in the study. **Result:** The study population was predominantly male, with most patients in their 40s and with good performance status. In this study, 73% of the patients had complete responses and 27% had partial responses. Patients with T2 stage disease showed a complete response, while some patients with T3 and T4 disease showed partial responses. The presence of multiple nodes and central hypoxia due to increased node size was associated with partial responses among patients with N2 disease. Stage III patients had a higher complete response rate than stage IV patients. Treatment delay due to toxicities occurred in 30% of patients, with most patients experiencing a treatment break of 1-3 days. **Conclusion:** The study suggests that most patients with hypopharyngeal and oropharyngeal malignancies respond well to treatment, with the tonsil subsite having the highest complete response rate.

INTRODUCTION

Head and neck cancers in India continue to be a major public health problem due to high exposure to smoking. Smoking tobacco among Indian people causes significant morbidity and mortality. Head and neck cancers comprise 5% of all malignancies worldwide.[1] The incidence is high in the countries of South East Asia, parts of Africa and South America.[2] The overall male-to-female ratio is 4:1. It usually occurs in the 5th decade. In India, they are among the top cancers affecting men and are the third most common cancers affecting women. In Tamil Nadu, MMTR states that the most common cancer in men is head and neck (19.23%) and almost 75% are present in the locally advanced stage. Therefore, multimodality treatment is the best option for treating squamous cell carcinoma of the head and neck. Altered fractionation schedules of RT lead to a 7% to 10% improvement in loco-regional control. This study was mainly based on combining chemotherapy with an Altered Fractionation regimen to get enhanced loco-regional control in the advanced setting.[3]

The concomitant Boost technique was chosen to increase the response rate without excessive toxicities and reduce the treatment time from 7 weeks to 5 weeks. Cisplatin and Paclitaxel were chosen as a weekly regimen to potentiate radiation's effects. Cisplatin is the drug that proved effective in meta-analyses with a dose of 200mg in 5 weeks, comparable to 3 weekly Cisplatin. By arresting the cells at the G2M phase, Paclitaxel increases the sensitising effects of radiation. The study was planned to increase the total dose within a short period with enhanced effects of low-dose chemotherapy without increasing the morbidity due to toxicities.

The main aim of this study was to evaluate the use of altered fractionation in the form of a Concomitant boost along with low-dose chemotherapy in the form of weekly CDDP and Paclitaxel. The Primary Objective was to assess the immediate loco-regional response rates and the Secondary Objective was to evaluate the acute toxicity to the treatment.

MATERIALS AND METHODS

This single-arm prospective study was conducted between January 2015 and August 2015 in the Department of Radiotherapy, Barnard Institute of Radiology & Oncology, Madras Medical College, Chennai. Thirty consecutive patients with histopathologically proven squamous cell carcinoma of the head and neck who were fit for inclusion criteria were recruited from the outpatient department in the study. Approval from the institute's ethical committee was obtained. All the patients enrolled in the study were informed about the merits and demerits of participating in this study and signed an informed consent form in their regional language, Tamil.

Inclusion criteria: Biopsy-proven newly diagnosed squamous cell carcinoma of the head & neck, primary tumour sites: oral cavity, oropharynx, hypopharynx, larynx, age 20- 60 years, stage III or IV locally advanced squamous cell carcinoma, previously not exposed to any chemo or radiotherapy, ECOG 0-1, and no major life-threatening comorbidities were included.

Pre-treatment workup included detailed history including presenting symptoms, history, personal and family history, complete physical examination by inspection and palpation followed by routine blood investigations. If indicated, upper aerodigestive tract evaluation by direct and indirect laryngoscopy, anterior and posterior rhinoscopy and endoscopy to know the extent of disease and rule out a second primary. Biopsy was done from the primary tumour or fine needle aspiration cytology from the metastatic lymph node.

Contrast-enhanced CT scan of the base of the skull to the root of the neck was done before initiating treatment and after six weeks of treatment for response assessment. Chest X-ray was done to rule out lung metastases. The staging was done based on the American Joint Committee staging manual 7th edition (for head and neck cancers). Nasogastric tube insertion was done if indicated. Dental prophylaxis includes scaling, filling and extraction for the oral cavity and oropharynx tumours if required. Weekly CBC, RFT and LFT were assessed before each cycle of chemotherapy.

30 locally advanced squamous cell carcinoma of head and neck cancer patients were selected consecutively from the outpatient department, who then underwent the pre-treatment workup as mentioned before. All 30 patients were treated with a Theratron Phoenix Tele Cobalt-60 machine. Strict immobilization was practised while irradiating the patient. Eligible patients are treated with radiotherapy using a concomitant boost technique consisting of 45gy/1.8gyper# /25# -5 weeks to a field composed of the tumour plus 2 cm clearance and involved nodes along with possible microscopic node. 22.5gy/ 1.5gy per# /15# to a field two given as a boost only to the small field, including primary and involved node at an interval of 6 hrs during the last three weeks of treatment to a total dose of 67.5 Gy within five weeks of treatment. Inj. Paclitaxel 20mg/m2 - day 1, 8 15, 22, 29 and Inj. CDDP 30mg/m2 – day 1,8,15,22,29 given 1 hr before radiotherapy.

Chemo radiotherapy-induced toxicity was assessed and graded using Common Toxicity Criteria version 4.03 and RTOG acute radiation morbidity scoring criteria. All patients were reassessed by clinical examination, ENT examination with laryngoscopy and a contrast-enhanced CT Neck six weeks after completion of concurrent chemoradiation. Response to treatment was described, which depends on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1 version) Criteria. Patients with complete responses were kept for follow-up. Patients with a partial response were assessed for salvage surgery and if not feasible, started on palliative chemotherapy.

RESULTS

Clinicopathological Parameters

Thirty patients enrolled in the study were from age 36yrs to 60yrs with good performance status. Most were in the 5th decade, followed by the 4th decade. There was a male preponderance in this study since males are highly exposed to common risk factors such as tobacco, alcohol etc., and the incidence is also high in males. One female patient with a chronic irritating ulcer due to a sharp tooth had given rise to carcinoma. The most common presenting symptom among the study population was dysphagia, followed by odynophagia since most are hypopharyngeal and oropharyngeal malignancies. In the subsite analysis, supraglottis and pyriform fossa constitute the maximum number of cases. Most of them had T3 disease and N2 nodal disease. Most of the patients in this study belonged to moderately differentiated histology.

Table 1: Demographic data of the study

		Frequency	Percentage
Gender	Male	27	90%
	Female	3	10%
Age group	31 – 40 yrs	4	13%
	41 – 50 yrs	10	33%

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	51 – 60 yrs	16	54%
ECOG	ECOG 0	17	57%
	ECOG 1	13	43%
Habits	Tobacco(smoking)	17	57%
	Tobacco (smokeless)	9	30%
	Alcohol	20	66%
	None	4	13%
Symptoms/Signs	Dysphagia	19	63%
	Odynophagia	16	53%
	Ulcer or growth	9	30%
	Neck swelling	8	26%
	Voice change	11	37%
	Pain	11	37%
Primary site	Oropharynx	9	30%
	Hypopharynx	8	27%
	Oral cavity	5	16%
	Larynx	8	27%
Subsite	Supraglottis	8	26.66%
	Tonsil	6	20%
	Post 1/3 tongue	3	10%
	Pyriform fossa	8	26.66%
	ANT 2/3 tongue	4	13.33%
	Hard palate	1	3.33%
T stage	T1	0	0
	T2	4	13.33%
	T3	17	56.67%
	T4	9	30%
Nodal stage	N0	4	13.33%
	N1	10	33.33%
	N2	16	53.34%
Stage grouping	Stage III	14	46.67%
	Stage IV A	16	53.33%
Histological Differentiation	Well-differentiated	9	30%
	Moderately differentiated	13	43.33%
	Poorly differentiated	8	26.67%
Response	Complete response	25	83.33%
	Partial response	5	16.67%
	Static response	0	0
	Progression	0	0

Response Analysis

In this study, 73% of the patients had complete responses and 27% had partial responses. There was no static response or progression. In this study, Oropharynx, Hypopharynx and supraglottis had an equal number of complete responses, followed by the oral cavity. Among the subsites involved, the tonsil shows the complete response in all patients.

Subsites with well-differentiated histology show a poor response when compared to others. Three patients of the T4 stage and two of the T3 stage showed partial response. All patients of the T2 stage showed complete response. Five patients with N2 disease showed partial response because of the increased number of nodes and the multiple-matted nature of nodes with central hypoxia due to increased node size.

Among the 14 patients in stage III, 13 showed complete response and 1 showed partial response. Stage IV patients had reduced complete response when compared to stage III. Treatment delay due to toxicities which caused prolongation of overall treatment time was analyzed for a response. There was treatment delay in 30% of the patients compared to 70% who proceeded without delay in overall treatment time. Among the 30% of the patients, most patients with 1-3 days treatment break had 83% complete response whereas only 62.5% had complete in case of treatment break for four days or more.

Skin reaction: In this study, 21 patients had Grade 1 skin reactions in dry desquamation and decreased sweating. Another seven patients had patchy moist desquamation, whereas only two patients had grade 3 confluent moist desquamation during the last week of the treatment. All patients were treated with aloe vera cream and were safe at the end of the treatment.

Mucositis: Among the study population, six patients developed grade 3 mucositis. One patient developed grade 4 mucositis for whom RT was suspended till it healed. The patient was on regular mouthwash, antibiotics and analgesics. Thirteen patients developed grade 2 mucositis and ten developed grade 1 mucositis. These were best managed with antibiotics and analgesics such as pain ointment.

Xerostomia: Some patients developed altered sensations of taste and hard sticky saliva during the treatment. Only five patients developed grade 2 reactions, 17 developed grade 1 reactions and the rest didn't have much effect.

Pharyngitis: Since many patients presented with dysphagia, many advised NG tube feeding from the beginning. During the treatment, 18 patients had grade 2 pharyngitis followed by 7 and 5 patients with grade 3 and grade 1 pharyngitis.

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Table 2: Distribution of responses among the patients

		Complete response	Partial response
Site	Oral cavity	3(60%)	2(40%)
	Oropharynx	8(88.89%)	1(11.11%)
	Hypopharynx	7(87.50%)	1(12.50%)
	Larynx	8(88.89%)	1(11.11%)
Subsite	Supraglottis	7(87.5%)	1(12.5%)
	Tonsil	6(100%)	0
	Post 1/3 tongue	2(66.67%)	1(33.33%)
	Pyriform fossa	7(87.5%)	1(12.5%)
	ANT 2/3 tongue	2(50%)	2(50%)
	Hard palate	1(100%)	0
Tumour stage	T1	0	0
	T2	4(100%)	0
	T3	15(88.24%)	4(11.76%)
	T4	6(66.67%)	3(33.33%)
Nodal stage	N0	4(100%)	0
	N1	10(100%)	0
	N2	11(68.75%)	5(31.25%)
Histological Differentiation	Well-differentiated	6(66.67%)	3(33.33%)
	Moderately differentiated	11(84.62%)	2(15.38%)
	Poorly differentiated	8(100%)	0
Stage grouping	Stage III	13(92.86%)	1(7.14%)
	Stage IV	12(75%)	4(25%)
ECOG	0	16(94.12%)	1(5.88%)
	1	9(69.23%)	3(30.77%)
Treatment break	Number		
1-3 Days	5	3(60%)	2(40%)
$\geq$ 4 Days	4	1(25%)	3(75%)

Toxicity assessment

Table 3: Acute Radiological Toxicity of the study

Acute toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Skin reactions	0	21 (70%)	7 (23.33%)	2 (6.67%)	0	0
Mucositis	0	10 (33.33%)	13 (43.34%)	6 (20%)	1 (3.33%)	0
Salivary glands	8 (26.67%)	17 (56.67%)	5 (16.67%)	0	0	0
Pharyngitis	0	5 (16.67%)	18 (60%)	7 (23.33%)	0	0
Laryngitis	0	6 (20%)	16 (53.33%)	8 (26.67%)	0	0

Laryngitis: Some of the patients developed cough and symptoms of dyspnoea. Some patients with advanced laryngeal cancers had tracheostomy tubes at the time of presentation in our department. Metal tracheostomy tube has been replaced with portex tracheostomy tube before starting radiotherapy. Grade 1, 2, 3 and laryngitis were found in 6, 16 and 8 patients.

Table 4: Systemic toxicity of the study

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	20 (%)	4	0	0
Vomiting	10	5	0	0

Systemic toxicity: The treatment-related systemic toxicity was assessed with CTCAE V 4.03 and presented. Only minor systemic toxicities occurred during the treatment. There is no diarrhoea or cardiac toxicity during the treatment.

Table 5: Haematological toxicity of the study

Haematological toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Anaemia	15(50%)	12(40%)	3(10%)	0	0
Leucopenia	23(76.67%)	4(13.33%)	3(10%)	0	0
Thrombocytopenia	0	0	0	0	0

Haematological toxicities: Anaemia: 15 patients had adequate Hb levels during the treatment. Twelve patients had Hb dropped between 11 and 9.5 gms and were given iron tablets. Only three patients had Hb less than nine gms in the third and fourth weeks of treatment and were given packed cell transfusions.

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Leucopenia and neutropenia: Leucopenia and neutropenia were found only in 7 patients during the treatment. They were given Inj G_CSF 300mg subcutaneously daily, antibiotics and homemade foods for three days. For this reason, the chemotherapy schedule was slightly altered, i.e., on the 4th day of the week.
Thrombocytopenia No thrombocytopenia was noted during the treatment among the study population.
Renal toxicity the patients had normal renal function tests throughout the treatment.

DISCUSSION

Most of the patients in India presented with an advanced stage to the hospitals due to their poor socioeconomic status, illiteracy and fear of neglect by their family and society. Head and Neck squamous cell carcinomas are becoming more prevalent in younger age groups, commonly below 40 years, due to increased smoking and smokeless tobacco in pan, gutka and ganja.[4] though most of them present in locally advanced stages, their performance status is still good because of their age. We are positioned to plan an intense treatment regimen with multimodality management to achieve better local and regional control and disease-free survival.

Altered fractionation with or without concomitant chemotherapy improves tumour control and survival outcomes compared with conventionally fractionated definitive RT alone for stage III-stage IV HNSCC. A study by withers et al. showed that accelerated repopulation usually occurs after 28 days of treatment for head and neck cancers. A dose increment of 0.6 Gy per day is necessary to compensate for this repopulation. RTOG 90-03 TRIAL compared altered fractionation schedules such as Hyperfractionation Vs Concomitant Boost RT Vs Split course RT to standard Conventional RT in locally advanced squamous cell carcinoma of the head and neck. They found 2- and five-year loco-regional control rates were better in Hyper Fractionated and Concomitant Boost arms than standard fractionation.[5] In a recent meta-analysis, enhanced LRC with modified fractionation translated into a 3.4% improvement in overall survival (OS) at five years.[6] A phase III Randomized trial in a single institution in India conducted by Ghoshal Patients treated with concomitant boost had a better 2-year disease-free survival (71.7% vs 52.17%, P=0.0007) and loco-regional control rates (73.6% vs 54.5%, P=0.0006) than with conventional fractionation.[7]

A recent update of the Meta-analysis of chemotherapy on head and neck cancer (MACH-NC) showed that adding chemotherapy along with radiation results in a 19 % reduction in risk of death and an 8% improvement in overall survival compared to radiation therapy alone.[8] Various Altered fractionation regimens helped improve local and regional control and disease-free survival due to the increased dose to the tumour without increasing the complications. Though the acute toxic effects are known to be slightly increased, they can be very well managed with the best supportive measures since they are not life-threatening. Also, the late toxic effects are very low compared to standard fractionation. This is best achieved with a hyper fractionation regimen and concomitant boost irradiation.[9]

Concurrent chemotherapy and radiation improved loco-regional control with minimally increased toxicities. In this study, we opted for concomitant boost irradiation to achieve an increased dose for tumour control and to shorten the treatment time from 6.3 weeks to 5 weeks, along with low-dose chemotherapy cisplatin and paclitaxel for radiosensitisation and increased therapeutic effect.[10]

In this study, 54% of the patients were in the 5th decade, followed by 33% and 13% in the 4th and 3rd decade, respectively. This is the usual presentation in most of the studies. 90% of the patients in this study were males, while only 10% constituted females. Since this regimen has to be well tolerated, patients with good performance status were only included in this study. Most of them were in ECOG performance status 0 and 1.

57% of males had the habit of smoking and 30% had the habit of pan chewing, leading to oral cavity and oropharynx cancers. Only four primary sites were included to compare the results of the treatment. Tumours such as nasopharynx, nasal, paranasal and salivary gland tumours behaved differently and were omitted. Among the primary sites, oropharynx, hypopharynx and laryngeal malignancies showed 87% – 88% complete response rates. Only 11% - 12% showed partial response. But in the case of oral cavity tumours, 60% had a complete response and 40% had a partial response. This may be attributed to an increase in the bulk of the disease.

As usually explained, stage III tumours show an increased complete response of 93%, whereas stage IV patients showed a complete response rate of 75%. But these results are far better when compared to conventional radiation, concomitant boost radiation alone and concomitant boost with cisplatin alone. This explains the superiority of this study over other similar studies.[11]

Mucositis was an important side effect that caused treatment delay during the 4th and 5th weeks of treatment. 20% of the study population had grade 3 mucositis and 3% had Grade 4 mucositis for whom RT was suspended until mucositis heals. They were best managed with antibiotics, analgesics and low-dose steroids. Haematological toxicities were a little more pronounced in this study. Only 10% of the patients needed a blood transfusion during the treatment. 23% of patients had grade 1 and 2 leucopenia, for which Inj G CSF was given subcutaneously for three days. RT has been suspended for grade 3 leucopenia.

There was no thrombocytopenia during this study, and systemic toxicity was much less. Only 16% of patients had grade 2 vomiting, managed with IV

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fluids and antiemetics. There was no renal toxicity or cardiac toxicity in this study. There were no treatment-related deaths in this study. Among the patients with partial response, two patients with a tumour in the anterior 2/3rd tongue were taken up for surgery and three patients not willing to have morbid surgery were taken up for palliative chemotherapy.

This study showed an increased tumour control rate of complete response of 83% compared to the study conducted by Ghosal, which showed a 71% complete response rate. Another study from our institute showed a 79% complete response rate. This may be attributed to the addition of weekly low-dose chemotherapy in this study. At the same time, grade 3 mucositis was only 23% compared to 35% in the other two studies.

Merits of the Study

Concurrent chemoradiation is the ideal management of stage III and stage IV head and neck SCC that has shown improved local and regional control with manageable acute toxicities. There is no increase in mortality or morbidity. Chemotherapy – cisplatin and paclitaxel given in low doses are acceptable by all patients.

Demerits of the Study

This is not a large randomised control study and the sample size is too small for statistical analysis. Long-term follow-up is needed to calculate survival benefits.

Future Perspective

Various concomitant boost trials are upcoming with conformal techniques and simultaneous integrated boost techniques. Many chemotherapy drugs are being used and evaluated along with radiation. Also, many targeted agents, such as EGFR inhibitors, are used along with radiation in the concurrent setting.

CONCLUSION

This study is designed for patients with good performance status with advanced disease to achieve maximum tumour control without causing mortality or morbidity. The study succeeded with a complete response rate of 83% and a partial response rate of 17%. But since this study has no long-term follow-up, disease-free survival and overall survival cannot be calculated. Large randomized trials compared to conventional RT have been planned for detailed analysis.

Though there is a significant improvement in local and regional control of the tumour, there are enhanced acute toxicities which can be well managed with the best symptomatic care. Therefore, selecting patients is very important in this study to complete the treatment protocol within the stipulated time. The main advantage is the reduction of treatment duration to 5 weeks, which is essential in centres with patient overload.

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