

Original Research Article**A prospective randomized study evaluating the role of oral
Curcumin along with chemoradiation in management of locally
advanced head and neck carcinoma**

Running title : A prospective randomized study evaluating the role of oral Curcumin along with
chemoradiation in management of locally advanced head and neck carcinoma

ABSTRACT

Aim of this study was to evaluate the role of Curcumin along with or without chemoradiation in the management of locally advanced head and neck cancers (LHNC) in terms of tolerability, toxicity and response. Sixty treatment naive histopathologically proved cases LHNC were included in this prospective randomized study. Material and methods : Patients were randomly assigned to receive radical external beam radiotherapy (EBRT) with weekly cisplatin and capsule Curcumin from the first day of EBRT till the completion in the dose of 1gm every 8 hourly (Group I/ Study Group) and EBRT with weekly cisplatin only (Group II/ Control Group). Results : There were lower grades of statistically insignificant hemoglobin(*grade 2 p value- 0.300*) and total leucocyte count (*grade 1 p value- 0.313*) , toxicities in group II in compared to group I during treatment. The acute skin and mucosal reactions were less in group I than group II without any statistically significant association during treatment and follow ups. Statistically significant less blood urea (*grade 1 p value- 0.019*) toxicities observed in group I, in compared to group II during treatment. There were statistically significant fewer grade 3 and 4 vomiting (*p value- 0.037*) in group II. At one year follow up 67% was disease free in group I in comparison to 56% in group II.

Conclusion: Curcumin, in management of LHNC, seems to decreases haematological, renal, skin and mucosal chemoradiation induced toxicities results in timely completion of intended treatment without any financial burden on patients and improves the disease control.

28 INTRODUCTION

29 Head and neck cancers are among the most common cancers in developing countries, especially in
30 Southeast Asia. Majority of these patients are diagnosed with locally advanced disease. This
31 resulted in high incidence of loco regional recurrence and treatment failures. Concomitant
32 chemoradiation is standard of care in inoperable cases of head and neck carcinoma. However this
33 treatment schedule associated with more treatment induced an acute and late adverse effect which
34 leads to treatment interruptions and thus prolonged treatment time. The prolongations of treatment
35 time have adverse effect on success of treatment.¹⁻³ Various strategies have been tried to increase
36 response and to reduce treatment related toxicities when integrate with chemotherapy and
37 radiotherapy and therefore increase outcome. Curcumin is widely tried drug in various diseases as
38 well as in various cancers.

39 Curcumin is commonly used in the Indian and Eastern Asia as spice commonly known as turmeric.
40 Various studies showed that curcumin is supposed to have properties of radiosensitization and
41 chemosensitization to tumors, and radioprotection and chemoprotection to normal organs thus;
42 helpful in decreasing the toxicity and increasing the efficacy profile of the regimen.⁴⁻⁶ Based on the
43 information and literature available so far this prospective study has been conducted to determine
44 the role of curcumin along with chemoradiation in the management of locally advanced head and
45 neck cancers in terms of tolerability, toxicity and local control.

46 MATERIAL AND METHODS:

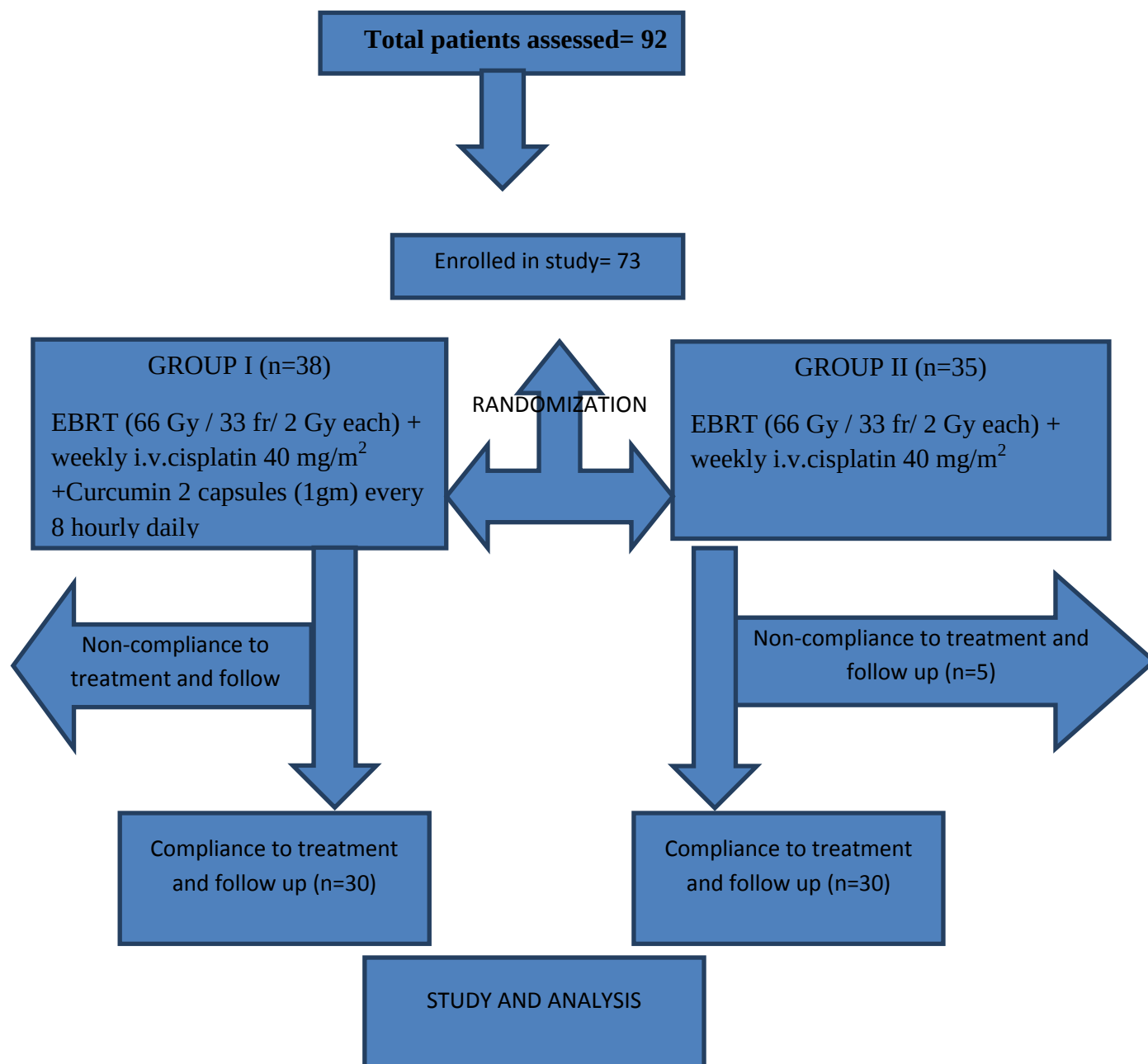
47 The study was carried out on locally advanced, histopathologically proven sixty (60) cases of
48 squamous cell carcinoma of Head and Neck region having stage III-IVB (AJCC-2010) disease
49 treated in Department of Radiotherapy, Pt. B. D. Sharma Postgraduate Institute of Medical
50 Sciences Rohtak (India), from May, 2013 to June, 2014. The patients included in study had
51 pretreatment Karnofsky performance status >70, hemoglobin >10mg/dl. Pretreatment complete
52 hemogram, kidney and liver function were within normal range. Chest X-ray and USG abdomen
53 showed no apparent metastatic disease. Patients with co-morbid disease and metastatic disease
54 were excluded from study.

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The patients were divided randomly in two groups of 30 patients each by draw of lots.



EBRT was delivered by Cobalt – 60 teletherapy machines. Assessment of toxicities was done weekly during treatment in both the groups as per WHO toxicity criteria, RTOG Acute Radiation Morbidity Scoring Criteria weekly during treatment and then monthly during follow up. Tumor response is assessed as per WHO response criteria. Disease status (clinically) and late radiation

toxicities (RTOG/EORTC criteria) assessed during last follow up at six months. Radiological examination, fine needle aspiration or biopsy was carried out in case of any suspicious clinical examination. All the patients were followed up monthly after completion of concurrent chemoradiotherapy and up to one year.

QUALITY ASSURANCE

Senior radiation oncologist in the department reviewed the records and also conducted examination of patients at random to verify treatment planning and findings of response and toxicities.

STATISTICAL ANALYSIS

Pretreatment patient and clinical characteristics between two groups were compared. For continuous variables, mean and median values compared between two groups. Endpoints of study were tumor & nodal response, and acute & late radiation toxicities. Subgroup analysis was carried out on various prognostic indicators. La Morte statistical software was used for data analyse. P value of <0.05 was considered as statistical significant.

Results: The base line patients and tumour characteristics in between the two groups were matching shown in Table 1. The mean age at presentation in group I and group II was 55.9 years and 56.7 years respectively. Overall, fifty five out of sixty (92%) patients were males, remaining five (8%) being females. Overall 93% patients were smokers (all more than 10 years history of smoking). Base of tongue was the most common primary site; 66.7% in the Group I and 76.6% in the Group II. The histopathological reports revealed that the most common histopathological type was moderately differentiated squamous cell carcinoma, being 83% in both groups.

111 Table 1 shows patients and tumour characteristics.

PATIENT CHARACTERISTIC		GROUP I	GROUP II
AGE (YEARS)	MEAN	55.9	56.7
	RANGE	40-85	32-70
GENDER	MALE	27	28
	FEMALE	3	2
SOCIAL BACKGROUND	RURAL	26	28
	URBAN	4	2
SMOKING HABBIT	SMOKER	29	27
	NON-SMOKER	1	3
CHIEF COMPLAINT	Difficulty in swallowing	10 (33.3%)	06 (20%)
	Pain in swallowing	03 (10%)	04 (13.3%)
	Pain Throat	08 (26.7%)	11 (36.7%)
	Neck mass	03 (10.0%)	04 (13.3%)
	Earache	02 (6.7%)	02 (6.7%)
	Change in voice	04(13.3%)	03 (10%)
SITE OF PRIMARY TUMOR	Oral cavity	02 (6.6%)	03(10%)
	Oropharynx	20(66.7%)	23 (76.6%)
	Hypopharynx	02 (6.7%)	02 (6.7%)
	Larynx	06 (20%)	02 (6.7%)
PRETREATMENT STAGE (AJCC2010)	Stage III	15 (50%)	14 (46.7%)
	Stage IV	15 (50%)	16 (53.3%)
HISTOPATHOLOGICAL	Well differentiated SSC	02 (6.7%)	05 (8.3%)
	Moderately differentiated	27 (90%)	23 (76.6%)
	SCC	01 (3.3%)	02 (3.3%)

TUMOR MORPHOLOGY	Poorly differentiated SCC		
	Ulcerative	16 (53.3%)	18 (60%)
	Indurative	03 (10.0%)	04 (13.3%)
	Proliferative	11 (36.7%)	08 (26.7%)
KPS (PRETREATMENT)	80	10 (33.3%)	10 (33.3%)
	90	20 (66.7%)	20 (66.7%)

112

113 Acute treatment induced grade III skin and mucosal toxicities observed 3.3% vs 20%;

114 and 10% vs 20% in group I and II respectively more in group II. However more Upper gastro-

115 intestinal toxicity (grade 3 and 4) was observed in group I (20%; 6.7%) v s (6.7%; 00%) in group

116 II. Hematological toxicity as fall in hemoglobin was seen less in group I patients- grade 3

117 toxicity: 00 % versus 3.33 % in group II. Grade 3 neutopenia was similar in both groups (3.33%).

118 Table 2: Toxicities

Toxicities	Group I	Group II
Haematological toxicities		
Hemoglobin		
Grade 2	02(6.66%)	03(10%)
Grade 3	-	01 (3.33%)
Total leucocyte count		
Grade 2	01(3.33%)	04(13.33%)
Grade 3	01 (3.33%)	01(3.33%)
Renal toxicities		
Blood Urea		
1	00	05 (16.66%)
2	-	
3	-	-
Serum Creatinine		
1	01 (3.33%)	
2	00	01(3.33%)

3	00	00
		00
Skin		
2	17(56.7%)	22(73.3%)
3	01 (3.33%)	06(20%)
Mucosal toxicities		
Grade 2	19(63.3%)	23(76.7%)
Grade 3	3(10%)	06(20%)
Upper Gastrointestinal		
toxicities(N/V)		
Grade 2	09 (30.0%)	07 (23.3%)
Grade 3	06 (20.0%)	02 (6.7%)
Grade 4	02 (6.7%)	00

119

120 In Curcumin group 90% patients completed indented treatment in 7.3 weeks in comparison to

121 80% in group II. Treatment was delayed in 10% by one week and completed in 8 -9 weeks. In

122 group II treatment interrupted in 20% for up to 2 weeks because of grade 3 skin reaction.

123 Intended treatment completed 8 – 9.5 weeks in group II.

124 Overall tumour and nodal response (Table 3) observed at one year of follow up showed 66.7%

125 showed no evidence of disease in group I, 56.7% in group II. Residual diseases seen in 16.6% vs

126 26.7% patients.

127 Table 3 Disease status at one year of follow up (locoregionally control – overall tumour and

128 nodal)

Group I	Disease Status			
	NED	RD	REC	PD
	20 (66.7%)	05 (16.66%)	03 (10%)	02(6.7%)
	17 (56.7%)	08 (26.7%)	04 (13.3%)	01(3.33%)

129 **NED=** No evidence of disease, **RD=** Residual disease, **REC=** Recurrent disease,

130 **PD=**Progressive disease

131 Patients were followed from May 2013 to June 2015. Mean duration of follow up was eighteen
132 months (range, 6 to 20); all patients were followed for at least for 12 months.

133 Late grade 1 and 2 skin toxicities were seen in 22/30 (73.3%) patients in group I and 25/30
134 (83.3%) patients in group II. There was no statistically significant association (*p value- 0.347*).

135 Late grade 1 and 2 late mucosal toxicities were seen in 19/30 (56.7%) patients in group I and
136 22/30 (73.3%) patients in group II (*p value- 0.405*). None of the patients experienced grade 3, 4
137 and 5 late skin and mucosal toxicity. In group I, grade 2 late salivary gland toxicities were seen
138 in 4 (13.3%) patients compared to 6 (20%) patients in group II (*p value- 0.488*). There were no
139 any grade 3, 4 and 5 late salivary gland toxicities in both the groups.

140

141 **DISCUSSION:**

142 To the best of our knowledge, this is first study that is evaluating the role of oral Curcumin along
143 with chemoradiation in locally advanced head and neck cancer.

144 In this study there were lower grades of haemoglobin (*grade 2 p value- 0.300*) and total
145 leukocyte count (*grade 1 p value- 0.313*) toxicities in group II in compared to group I during
146 treatment though statistically insignificant. As well as less blood urea (*grade 1 p value- 0.019*)
147 toxicities in group I, in compared to group II observed at third week of treatment.

148 Ueki et al studied the effect of curcumin administration (100 mg/kg ip) on the
149 inflammatory mechanisms involved in the pathogenesis of cisplatin-induced renal injury in mice.
150 Curcumin prevented cisplatin-induced tubular necrosis, decreased renal dysfunction and the
151 increase of pro inflammatory markers including of TNF- α in serum, and TNF- α and MCP-1 in
152 renal tissue, and a rising of intracellular adhesion molecule 1 (ICAM-1) mRNA in kidney.
153 Oxidative stress has been proven to be involved in Cisplatin induced toxicity including
154 nephrotoxicity. It is hypothesized that the reno-protective effects of curcumin may be related to
155 its predisposition to scavenge free radicals, and upregulate antioxidant machinery in kidney
156 mitochondria.⁷

157 Possibly these protective mechanisms of curcumin on kidney may be related to less cisplatin
158 induced renal toxicities in patients in group I in comparison to group II.

The acute skin and mucosal reactions were less in group I than group II without any statistically significant association. The statistically significant fewer grades 3 and 4 vomiting (p value-0.037) were observed in group II. It is generally recognized that curcumin does not cause significant short-term toxicity at doses up to 8 g day⁻¹; this dose of curcumin is considered suitable for trials in which curcumin is administered for short periods of time. Studies have shown that curcumin at doses ranging from 0.9 to 3.6 g day⁻¹ for 1–4 months have some adverse effects including nausea and diarrhoea.⁸

The onset and intensity of occurrence of severe reactions is significantly lesser in the study group. This is similar to the results observed by Ryan et al in breast cancer patients. Ryan et al conducted a randomized, double-blind, placebo-controlled clinical trial to assess the ability of curcumin to reduce radiation dermatitis severity in 30 breast cancer patients. Radiation dermatitis occurs in approximately 95% of patients receiving radiotherapy (RT) for breast cancer. Eligible patients were adult females with noninflammatory breast cancer or carcinoma *in situ* prescribed RT without concurrent chemotherapy. Randomized patients took 2.0 grams of curcumin or placebo orally three times per day (i.e., 6.0 grams daily) throughout their course of RT. Weekly assessments included Radiation Dermatitis Severity (RDS) score, presence of moist desquamation, redness measurement, McGill Pain Questionnaire-Short Form and Symptom Inventory questionnaire. The 30 evaluable patients were primarily white (90%) and had a mean age of 58.1 years. Standard pooled variances t test showed that curcumin reduced RDS at end of treatment compared to placebo (mean RDS = 2.6 vs. 3.4; P = 0.008). Fisher's exact test revealed that fewer curcumin-treated patients had moist desquamation (28.6% vs. 87.5%; P = 0.002). No significant differences were observed between arms for demographics, compliance, radiation skin dose, redness, pain or symptoms. In conclusion, oral curcumin, 6.0 g daily during radiotherapy, reduced the severity of radiation dermatitis in breast cancer patients.⁹

Curcumin is supposed to have properties of radioprotection and chemoprotection to normal organs thus, helpful in decreasing the toxicity profile of the regimen. Administration of curcumin in patients is able protect normal cells against the harmful effects of radiation.⁶

Electronic databases (Medline, PubMed, and CancerLit) and reference lists of published reports, review articles, and relevant books were searched. Clinical trials of curcumin evaluating

188 the skin reactions are not available in literature for head and neck carcinoma. So, direct
189 comparison was not possible.

190 For all stages, the no evidence of disease (NED) at the last follow up at one year in group
191 I and group II were: 20 (66.7%) versus 17/30 (56.7%).

192 In study on the potential cooperative effect of cisplatin and curcumin, two HNSCC cell lines (*In*
193 *vivo* study) were treated with curcumin or cisplatin alone or in combination. Cisplatin treatment
194 led to cellular senescence, indicating an effect mediated by p53 activation. The mechanisms of
195 the two agents through different growth signaling pathways suggest potential for the clinical use
196 of sub therapeutic doses of cisplatin in combination with curcumin, which will allow effective
197 suppression of tumor growth while minimizing the toxic side effects of cisplatin.¹⁰

198 As per Radiation Therapy Treatment Oncology (RTOG) and the European Organization
199 for Research and Treatment of Cancer (EORTC) criteria late radiation toxicities were observed
200 during follow up at six months of each patient.

201 Patients were followed from May 2013 to June 2015. Mean duration of follow up was
202 eighteen months (range, 6 to 20); all patients were followed for at least 12 months.

203 Late grade 1 and 2 skin toxicities were seen in 22/30 (73.3%) patients in group I and 25/30
204 (83.3%) patients in group II. There was no statistically significant association (*p value*- 0.347).
205 Late grade 1 and 2 late mucosal toxicities were seen in 19/30 (56.7%) patients in group I and
206 22/30 (73.3%) patients in group II (*p value*- 0.405). None of the patients experienced grade 3, 4
207 and 5 late skin and mucosal toxicity.

208 It may be inferred from studies that possible radioprotective, chemoprotective, anti-
209 inflammatory, antioxidant, wound-healing, antimicrobial, analgesic and antiseptic activities of
210 curcumin preventing acute skin and mucosal reactions may possibly also related to
211 comparatively less late skin, mucosal and salivary gland toxicities in patients receiving
212 curcumin. Keeping in view the high chances of treatment induced mucositis which result in
213 treatment interruptions; curcumin may be effective in prevention of mucositis and hence may
214 help in the timely completion of the intended treatment.

215 Therefore, it may be concluded from the present study that Curcumin, in management of locally
216 advanced head and neck carcinoma, decreases haematological, renal, skin and mucosal

chemoradiation induced toxicities and less treatment interruption which also help in improvement the disease control. However, upper gastrointestinal toxicity in terms of vomiting is significant. To further explore and establish the role of Curcumin in management of locally advanced head and neck carcinoma, a larger study with more number of patients is needed.

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