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PALLIATIVE CHEMORADIOTHERAPY VERSUS RADIOTHERAPY ALONE FOR MANAGEMENT OF LOCALLY ADVANCED HEAD & NECK CARCINOMA PATIENTS WITH POOR PERFORMANCE STATUS

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Abstract: **Introduction:** Palliative external beam radiotherapy (EBRT) and chemotherapy is commonly practiced for management of locally advanced head & neck carcinoma (LAHNC) patients with poor performance status. This study compares EBRT alone and EBRT along with low dose Gemcitabine.
Method: Study was conducted in Department of Radiotherapy, PGIMS Rohtak, in 2008-09; on histopathologically proven, untreated 60 cases of LAHNC, having KPS 60-70. Patients were randomly assigned either control group (n=30), given EBRT alone as 20Gy/5Fr/5days or study group (n=30), given EBRT as 20Gy/ 5Fr/ 5days and Gemcitabine 200 mg/m^2 i.v. 2 hour prior to radiotherapy on day 1. Mean age was 53 years (26-84 years). Male:Female ratio was 5:1. Most common primary site was base of tongue followed by larynx. Major symptoms were pain, difficulty in swallowing and altered voice. Patients were staged as per AJCC 2002; 2/3rd were stage IVA and 1/3rd were IVB. Despite randomization, there was no significant difference between two groups in age, sex, primary site, stage, and performance status. The side effects were graded as per RTOG criteria.
Results: Objective response, 3 months post-treatment, in the chemo radiotherapy and radiotherapy alone group respectively was: CR 7% vs 0%; PR 30% vs. 33%; stable disease 56% vs 46% and progressive disease 7% vs 20%. Subjective response similarly was better in study group throughout; even significantly better in dysphagia at 3 months follow up. Acute skin reactions were: Grade I- 73% vs. 47% at 2 weeks and 60% vs. 40% at 1 month respectively. Acute mucosal reactions were: Grade I- 30% vs. 17%, Grade II- 43% vs. 17% respectively. No hematological and grade III/IV skin or mucosal reactions observed. Differences in reactions were not statistically significant.
Conclusion: In management of LAHNC patients with poor performance status, addition of low dose Gemcitabine to palliative radiotherapy gives better disease control and symptomatic relief without unmanageable side effects.

Locoregionally advanced disease, in patients of head and neck carcinoma, is usually inoperable and symptoms are very prominent. Hence, local palliation is undertaken, if the patient is not suitable for aggressive intervention. The goals of ideal palliation include optimal symptomatic relief, tumor response, low toxicity and minimization of the time spent in a health care facility.

This study aims to assess the feasibility and efficacy of Gemcitabine and Palliative radiotherapy in symptomatic management of locally advanced incurable head and neck carcinoma and express in terms of disease control, symptom relief and toxicity.

MATERIAL AND METHOD

Patients

Between 2008 and 2009, sixty treatment naeve, histopathologically proven patients of LAHNC (Stage IV, non-metastatic) attending the Department of Radiotherapy, Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak (India) were taken up for palliative treatment by radiation therapy with or without chemotherapy. The patients had Karnofsky performance status 70 to 60, hemoglobin >10gm/dl, normal neutrophil & platelet counts, and liver & kidney function tests within normal range. Chest x-ray and USG abdomen showed no apparent metastatic disease. The inoperable status was conjointly defined as (i) primary tumor extension/invasion to surrounding region or tumor of sites considered unsuitable for oncological clearance; (ii) nodal status where neck dissection would not achieve control.

Radiation

All patients were planned for palliative radiotherapy with Cobalt teletherapy machine and simulated on Simulator CT. Intended radiation treatment for all patients was 20Gy in 05 fractions over 01 week (one daily fraction of 400cGy).

Chemotherapy

The patients were randomly assigned (by draw of lots) either of two groups; I (Control)- the radiotherapy only group or II (Study)- the chemoradiotherapy group, to be given Gemcitabine 200 mg/m^2 i.v. 2 hour prior of radiotherapy on day one of radiotherapy.

Evaluation

After completion of treatment follow up of cases was done after two weeks and then, monthly for 3 months for symptoms relief like pain, dysphagia, cough, insomnia and dyspnoea. Evaluation of symptom control was done by simple method of Indian rupee scale (1 rupee = 100 paise) describing relief in percentage, from no relief= 0 paise to corresponding paise/ percentage relief. The disease response (both primary and nodal response) was assessed according to WHO criteria and toxicity according to RTOG criteria. Patient characteristics are shown in Table 1.

Quality assurance

The study was carried out; only after the protocol was approved by the institution's ethics review board. Senior radiation oncologists in the department reviewed the records and also conducted examination of the patients at random, to verify the findings of response & toxicity.

Statistical analysis

This was a randomized trial with 1:1 allocation ratio by means draw of lots randomization. Frequency tables with counts and percentages were used to describe pre-treatment and treatment characteristics for each group. The categorical clinical characteristics between the two treatments were compared. For continuous variables, mean and median values were compared between the groups. Endpoints included Symptom-relief, tumor & node response and toxicity. Data were analyzed using the statistical software La Morte and *p*-value of <0.05 was taken as significant.

Table 1: Patient characteristics

Characteristics		Group I	Group II
Age (years)			
	≤40	05 (16.7%)	06 (20.0%)
	41-60	18 (60.0%)	17 (56.7%)
	61-80	07 (23.3%)	06 (20.0%)
	>80	00 (00.0%)	01 (03.3%)
Gender			
	Males	24 (80.0%)	26 (86.7%)
	Females	06 (20.0%)	04 (13.3%)
Social background			
	Rural	25 (83.3 %)	20 (66.7 %)
	Urban	05 (16.7 %)	10 (33.3 %)
Smoking habit			
	Smoker	29 (96.7 %)	26 (86.7 %)
	Non-smoker	01 (3.3 %)	04 (13.3 %)
Chief complaints			
	Difficulty in swallowing	10 (33.3%)	12 (40.0%)
	Pain in swallowing	06 (20.0%)	06 (20.0%)
	Neck mass	08 (26.7%)	08 (26.7%)
	Non-healing ulcer	02 (6.7%)	01 (3.3%)
	Earache	03 (10.0%)	01 (3.3%)
	Altered voice	01 (3.3%)	02 (6.7%)
Site of primary tumor			
	Ant. Tongue	01 (3.3%)	02 (6.7%)
	Floor of Mouth	01 (3.3%)	01 (3.3%)
	Retromolar Trigone	03 (10.0%)	00
	Tonsil	02 (6.7%)	02 (6.7%)
	Base of Tongue	19 (63.3%)	15 (50.0%)
	Soft Palate	00	00
	Hypopharynx	02 (6.7%)	05 (16.7%)
	Larynx	02 (6.7%)	05 (16.7%)
Stage (AJCC 2002)			
	IV A	20 (66.7%)	19 (63.3%)
	IV B	10 (33.3%)	11 (36.7%)
Histopathology			
	Well Differentiated SCC	01 (3.3%)	02 (6.7%)
	Moderately Differentiated SCC	26 (86.7%)	24 (80.0%)
	SCC, not otherwise specified (NOS)	03 (10.0%)	04 (13.3%)
Tumor Morphology			
	Ulceroproliferative	28 (93.3%)	30 (100%)
	Infiltrative	02 (06.7%)	00 (0.0%)
KPS			
	70	17 (56.7%)	22 (73.3%)
	60	13 (43.3%)	08 (26.7%)

RESULTS

A- Locoregional Control

Locoregional response at primary disease, nodal site and overall (Primary + Node) is shown in Tables 2, 3, 4 and Figures 1, 2, 3.

Table 2: Loco-Regional Control at primary site (n=60)

Objective response (Primary site)								
	Control	Study	Control	Study	Control	Study	Control	Study
	2 Weeks		**1 Month**		**2 Month**		**3 Month**	
CR	1(3%)	1(3%)	1(3%)	2(7%)	2(7%)	4(13%)	1(3%)	4(13%)
PR	11(37%)	11(37%)	13(43%)	16(53%)	12(40%)	14(47%)	13(44%)	13(43%)
NC	18(60%)	18(60%)	16(53%)	12(40%)	12(40%)	12(40%)	10(33%)	13(43%)
PD	0	0	0	0	4(13%)	0	6(20%)	0
CR	*p= 1*		*p> 0.5*		*p> 0.38*		*p> 0.16*	
PR	*p= 1*		*p >0.43*		*p> 0.6*		*p = 1*	

PR- Partial Response; CR- Complete Response; NC- No Change; PD- Progressive Disease

Table 3: Loco-Regional Control at nodal site (n=60)

Objective response (Node)								
	Control	Study	Control	Study	Control	Study	Control	Study
	2 Weeks		**1 Month**		**2 Month**		**3 Month**	
CR	3(10%)	5(17%)	4(13%)	9(30%)	4(13%)	9(30%)	4(13%)	10(33%)
PR	9(30%)	9(30%)	11(37%)	7(23%)	12(40%)	6(20%)	10(33%)	5(17%)
NC	15(50%)	14(47%)	12(40%)	12(40%)	11(37%)	12(40%)	12(40%)	12(40%)
PD	0	0	0	0	1(3%)	1(3%)	2(7%)	2(7%)
CR	*p >0.4*		*p > 0.1*		*p > 0.1*		*p = 0.066*	
PR	*p = 1*		*p > 0.26*		*p = 0.075*		*p > 0.13*	

Table 4: Loco-Regional Control Overall (n=60)

Objective response (Tumor + Node)								
	Control	Study	Control	Study	Control	Study	Control	Study
	2 Weeks		**1 Month**		**2 Month**		**3 Month**	
CR	0	0	0	0	0	2(7%)	0	2(7%)
PR	6(20%)	7(23%)	9(30%)	12(40%)	11(37%)	9(30%)	10(33%)	9(30%)
NC	24(80%)	23(77%)	21(70%)	18(60%)	14(46%)	18(60%)	14(46%)	17(56%)
PD	0	0	0	0	5(17%)	1(3%)	6(20%)	2(7%)
CR	*P= 1*		*P= 1*		*p = 0.39*		*p = 0.39*	
PR	*p = 0.5*		*p = 0.29*		*p = 0.24*		*p = 0.24*	

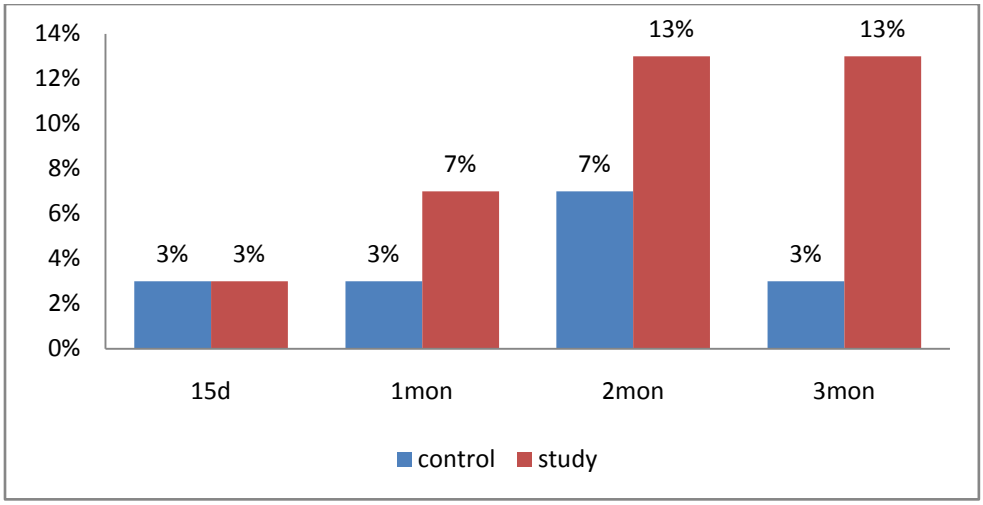

Figure 1- Loco-regional control at primary site (CR_T)

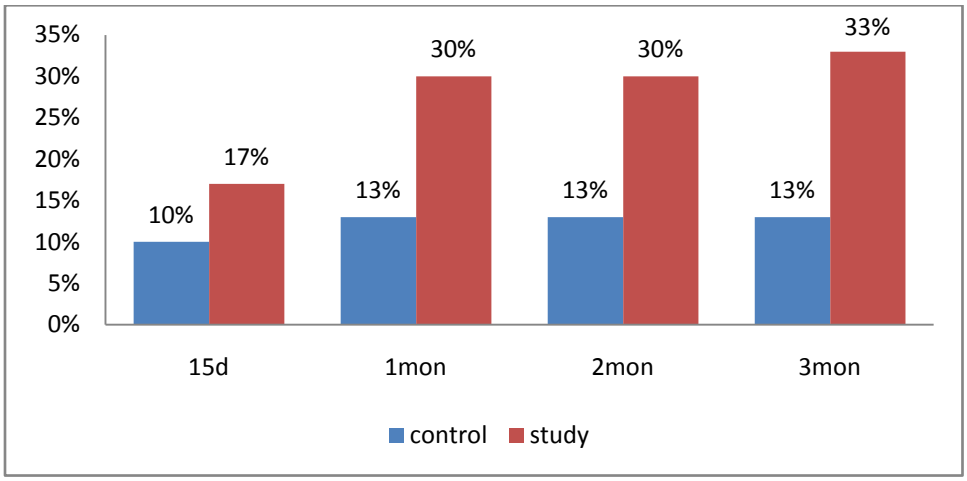

Figure 2- Loco-regional control at nodal site (CR_N)

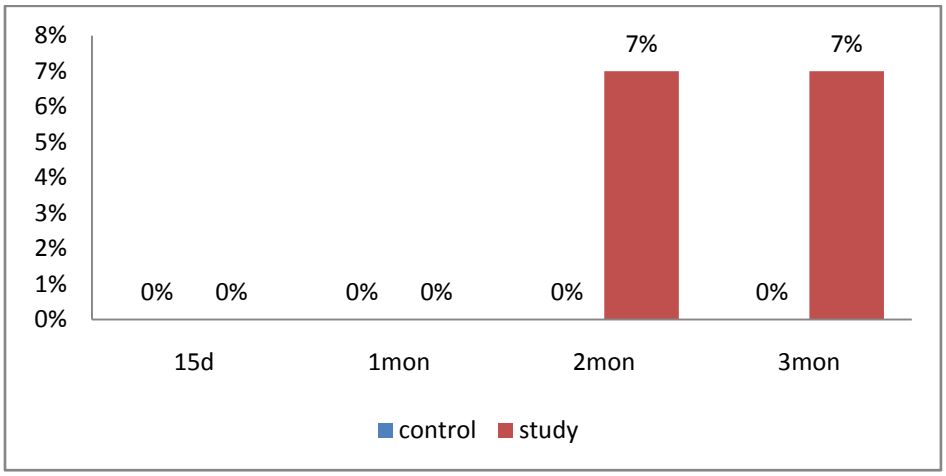

Figure 3- Loco-regional control Tumor + Node (CR_{T+N})

B - Subjective response

Symptomatic relief at 3 months of follow-up

Symptomatic relief after three months of follow-up is summarized in Table 5 and Figure 4. Significantly good response was observed in study group, especially in more common symptoms like difficulty in swallowing (dysphagia) and pain.

Table- 5: Symptomatic relief at 3 months of follow-up (n=60)

Subjective response								
	Control	Study	Control	Study	Control	Study	Control	Study
	Pain		Dysphagia		Tongue movement		Hoarseness of voice	
Total no.	23(77%)	22(73%)	21(70%)	24(80%)	6(20%)	7(23%)	9(30%)	20(67%)
0%	7(30%)	6(27%)	6(29%)	5(21%)	5(83%)	2(29%)	1(10%)	6(31%)
<50%	6(26%)	2(9%)	11(52%)	4(17%)	0	2(29%)	4(45%)	6(31%)
>50%	10(44%)	14(67%)	4(19%)	15(62%)	1(17%)	3(42%)	4(45%)	8(38%)
	p= 0.14		***p= 0.003***		***p= 0.34***		***p= 0.56***	

Subjective response								
	Control	Study	Control	Study	Control	Study	Control	Study
	Trismus		Ulcer		Bleeding		Earache	
Total no.	4(13%)	2(7%)	2(7%)	3(10%)	2(7%)	5(17%)	3(10%)	1(3%)
0%	2(50%)	1(50%)	1(50%)	2(67%)	0	0	2(67%)	0
<50%	2(50%)	0	1(50%)	1(33%)	1(50%)	1(20%)	1(33%)	1(100%)
>50%	0	1(50%)	0	0	1(50%)	4(80%)	0	0
	p= 1		***p= 1***		***p= 1***		***p= 1***	

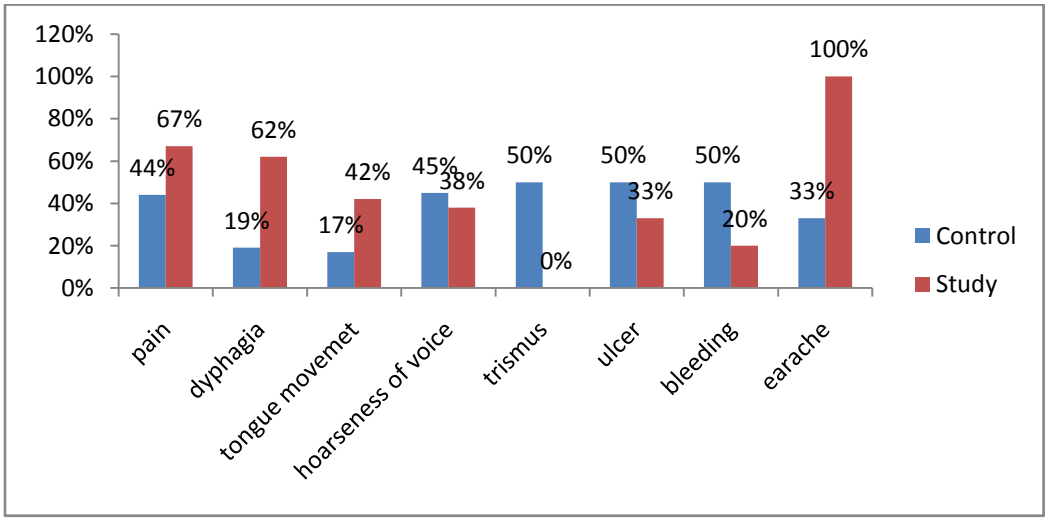

Figure 4- Symptomatic relief at 3 months of follow-up

C- Skin Reactions

The acute effects of radiation on skin were noted daily during and after the treatment. After two weeks 73% of study group and 47% of control group and at one month 60% of study group and 40% of control group developed mild skin color change and epilation in the radiation field (Grade I), and then on subsequent follow up no skin reactions were observed. The difference in the two groups is not statistically significant ($p > 0.1$).

D - Mucosal Reactions

The acute effects of radiation on mucosa were noted daily during the treatment and then after the treatment, during follow up. No mucosal reactions were noticed during treatment. After two weeks of completion of treatment 30% of patients in the study group and 17% in the control group developed grade-I mucosal reactions and 43% of patients in the study group and 30% in the control group developed grade-II mucosal reactions. On subsequent follow ups no reactions were noticed. The difference in the two groups for mucosal reactions are not statistically significant (for grade I reaction $p > 0.4$, and for grade II reaction $p > 0.6$).

DISCUSSION

Cancer of the head and neck is a term used to describe neoplasms that arise from the surface mucosa of the upper aerodigestive tract. The majority of head and neck cancer patients (70% to 80%) are diagnosed having locally advanced disease with lymph node involvement in up to 30%-35% cases.[1] Five-year survival, even with aggressive treatment (after curative treatment with surgery, radiotherapy alone or concomitant chemoradiation) is less than 20%, with a median survival of around 12 months.[2]

In patients with advanced disease, symptoms are very prominent and local palliation is undertaken, if the patient is not suitable for aggressive intervention. Aggressive chemoradiotherapy and/or altered fraction radiotherapy regimens have not, till date, yielded satisfactory results and survival.[3]

Patients with poor performance status cannot tolerate curative protocol with surgery, radiotherapy alone or concomitant chemoradiation, due to toxicity and prolong duration of treatment. The goal of treatment becomes achieving the best result with shortest possible treatment.[4]

The factors that should guide the treating oncologist in choosing patients for palliative intent treatment are- i) inoperable, fixed and unresectable disease; ii) very advanced loco-regional disease not amenable to cure; iii) poor physical condition and medical co-morbidities; iv) widely metastatic disease; v) achievable symptomatic relief; and vi) short life-expectancy. There is a paucity of guidelines in current literature regarding the optimal choice of palliative radiotherapy regimens for these patients with inadequate information on time, dose and fractionation; toxicity of such palliative regimens; and quality of life (QOL) issues pertinent to them.[5, 6]

In the last decade or so, clinical trials and consensus guidelines utilizing short-course palliative radiotherapy (PRT) have evolved for several incurable solid tumors such as bone metastases, brain metastases and lung cancers. Only few trials have been done in advanced incurable squamous cell carcinoma of head and neck (SCCHN). It has been suggested that higher dose of RT is needed for growth restraint and sustained palliation in head and neck cancers. Although the quality of evidence is not very robust, the weight of evidence favors short course of fractionated regimen (20 Gy/5F or 30Gy/ 10F) or cyclic treatment (QUAD SHOT) as compared to single or protracted course of radiotherapy.[7-9]

The palliative radiotherapy schedule of 20 Gy/5F in one week is probably the simplest schedule and is so commonly followed that it has almost become a standard of care for the palliative care of incurable head and neck carcinoma. Persual of the literature also shows some advantage of chemoradiation in the palliative setting.[10, 11]

Gemcitabine is a nucleoside analogue with excellent clinical activity against solid tumors. Within the cell, gemcitabine is rapidly phosphorylated to its active di-and triphosphate metabolites. Cytotoxicity with gemcitabine appears to be related to multiple effects on DNA replication, where gemcitabine triphosphate can serve as both an inhibitor and substrate for DNA synthesis.[12]

Gemcitabine diphosphate inhibits ribonucleotide reductase, producing decreases in cellular dNTP (deoxy nucleotriphosphate) pool levels in a cell-specific manner. These two major characteristics of gemcitabine, reduction in cellular dNTP pools and incorporation into DNA, are features of other antimetabolites antitumor agents which also exhibit radiosensitizing properties. Based on these favorable metabolic characteristics and the clinical activity of gemcitabine in tumor types which are commonly treated with radiation, the ability of gemcitabine to enhance radiation induced cytotoxicity has been evaluated. Gemcitabine was most effective as a radiosensitizer when administered at least 2 hours prior to irradiation.[13]

Even at very low concentrations, gemcitabine has been shown to be a powerful radiation sensitizer. At doses well below those used to produce cytotoxicity, radiation enhancement ratios as high as 1.6 have been observed. The dose of gemcitabine varies from 800 mg/m^2 to 1000 mg/m^2 when it is used as cytotoxic chemotherapeutic agent and from 50 mg / m^2 to 300 mg / m^2 when used as radiosensitizer.[14, 15]

As gemcitabine is radiation sensitizer even at low concentration and without any significant toxicity, the radiation in the dose of 20 Gy in 5 fractions has been used with it, in an attempt to improve response rate and the palliation of advanced incurable head and neck cancers.

The study has revealed that addition of low dose Gemcitabine, concomitant with palliative radiotherapy resulted in better locoregional control and symptom relief, acceptable toxicity profile and with no prolongation of overall treatment time.

Hence it may be concluded from this study that, in management of LAHNC patients with poor performance status, addition of low dose Gemcitabine to palliative radiotherapy gives better symptomatic control, without unmanageable side effects. Moreover, regimen suits well for busy oncology setups with patient load of locally advanced cases, not amenable to radical treatment.

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