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Induction Chemotherapy Followed By Concurrent Chemoradiotherapy Versus Radiotherapy Alone In Locally Advanced HNSCC – An Experience From Medical College In West Bengal, India

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ABSTRACT

Introduction*:*

Locally advanced Head and neck cancers (LAHNSCCs) are emerging as an important public health issue in India. Our study was designed to provide NACT to LAHNSCC patients followed by comparison between chemoradiation versus only radiation in rural medical college.

Material and Method*:*

Histopathologically proven non-metastatic LAHNSCC were randomized into 2 arms. Patients in both arms initially received 3 cycles of NACT (inj Paclitaxel 175mg/m^2 and inj Carboplation AUC 6, i.v, q 21 days). Thereafter they received definitive treatment accordingly: arm A (control arm) received conventionally fractionated radiotherapy (CFRT), 70 Gy in 35 # and in arm B (study arm) received conventionally fractionated radiotherapy (CFRT), 70 Gy in 35 # with concomitant 3 weekly cisplatin 100mg/m^2. A RECIST v1.0 criterion was used for response assessment and toxicities evaluated by RTOG Acute and late Morbidity scorings.

Results*:*

Between July 2013 to December 2015, 140 patients were randomized into arms. Laryngeal and hypopharyngeal subsites together accounted for 36.4% patients. 70% of patients were in AJCC TNM 7^{th} edition stage IV. 87.8% of patients completed the planned 3 cycles of NACT. Response assessment using RECIST v1.0 criteria after NACT were comparable in both arms with CR in 25% patients and PR in another 60% patients, p value 0.963. After completion of full treatment, 68.57% (48/70) patients in concurrent arm had CR against 55.72% patients (39/70) in only radiation arm, p value 0.241. At the end of study, 38 patients in arm A and 46 patients in arm B were eligible for response assessment. 24 patients (63.2%) in arm A were in complete response against 32 patients (69.6%) in concurrent chemoradiation arm, p value 0.535. Gastrointestinal and mucositis grade 3 toxicities were significantly increased in concomitant chemoradiation arm.

Conclusion*:*

Our study failed to show any statistical significant improvement in CR in favour of CTRT arm in our subset of patients. Yet definitive conclusion regarding use of only radiation cannot be made for LAHNSCC especially when combined with induction chemotherapy.

Keywords: Concurrent Chemoradiation, Radiation, HNSCC

INTRODUCTION

Head and neck cancers (HNCs) are emerging as an important public health issue not only in India but worldwide. The annual worldwide incidence is 5,50,000 [1] with India having reported cases of 122,643 males and 53,148 female patients in 2010.[2] Taikar *et al.* predicted increase in HNCs to 153,636 for males and 64,785 females by 2020.[2] HNSCCs account for 30% in males and 11-16% in females of all sites of cancers in this country. Around 75% of the cases in India are diagnosed in locally advanced stage.[3] Squamous cell carcinoma (SCC) is the most frequent histological type in head neck cancer including all subsites. The treatment gets complicated by advanced stages of disease presentation and co-morbidities with limit the conventional and established treatment modalities. According to the MACH NC meta-analysis benefit of chemotherapy in concomitant and neoadjuvant settings have been established.[4-6] Neoadjuvant chemotherapy aims to reduce the initial bulk of disease with organ preservation, alleviating the symptoms and improving the quality of life. In addition NACT is beneficial in better control of distant metastases. This was rationality for using NACT in study. But the when coming to definitive treatment, chemoradiation or only radiation still remains unclear for subset of inoperable LAHNSCC patients presenting with bulky and fixed primary / nodal disease or complicated with co-morbidities. In our medical college these patients account for 60-70% of HNSCC. So 'only radiation' was used as an alternative to chemoradiation for these patients inspite of studies showing the improved benefits with chemoradiation. Our study was designed to provide NACT to patients recruited in the study followed by comparison between chemoradiation versus radiation in rural medical college.

MATERIALS AND METHOD

Histopathologically proven non-metastatic LAHNSCC attending Radiotherapy Outpatients Department of Medical College and Hospital were assigned for this prospective study based on CONSORT study design. Eligibility criteria included patients of either sex, older than 18 years upto 70 years with normal baseline complete blood count(Hb > 10 gm/dl, ANC > 1500/µl, platelets > 100,000/µl,), liver and renal function tests (total serum Bilirubin<1.5 mg/dl and serum creatinine<1.5mg/dl), histopathologically proven head and neck squamous cell carcinoma, ECOG performance status 0-2, locally advanced disease (stage III & IVA, according to the AJCC 7th edition staging manual and no evidence of any prior anti malignant therapy or surgery (except biopsy from primary site) or coexisting synchronus or previous second malignany. However malignancies originating from the nasopharynx, paranasal sinus, salivary gland, thyroid and external auditory canal were not taken into account. Patients were randomized into 2 arms upfront. Patients in both arms initially received 3 cycles of inj Paclitaxel 175mg/m^2 and inj

Carboplation AUC 6, i.v, q 21 days. Thereafter they received definitive treatment accordingly: arm A (control arm) received conventionally fractionated radiotherapy (CFRT), 70 Gy in 35 # and in arm B (study arm) received conventionally fractionated radiotherapy (CFRT), 70 Gy in 35 # along with concomitant 3 weekly cisplatin 100mg/m^2. A RECIST v1.0 criterion was used for response assessment post treatment and 3 monthly till end of study and toxicities evaluated by RTOG Acute and late Morbidity scorings. The data was collected in predesigned worksheet and analyzed using Microsoft Excel Office 2007 and SPSSv17, IBM Corp, Chicago. The study was conducted according to Helsinki protocol and after institutional ethical committee approval.

RESULTS

Between July 2013 to December 2015, histopathologically proven non-metastatic LAHNSCC were assigned for this prospective study.(Figure 1) Number of patients eligible for analysis was 140 equally distributed into two treatment arms. 70% of patients were in age group of 41 -60 years, with males accounting for 117 /140 (83.5%). 85% (119/140) of patients were Hindu with Muslims accounting for remaining numbers. Tobacco as only addiction accounted in 67.14% patients followed by alcohol as next important addiction factor, highlighting the synergistic action of the addiction in carcinogenesis. Laryngeal and hypopharyngeal subsites together accounted for 36.4% patients. 70% of patients were in AJCC TNM 7th edition stage IV. (Table 1) However no subset analysis was made according to TNM sub-grouping and anatomical sites of involvement. 87.8% of patients completed the planned 3 cycles of NACT. Response assessment using RECIST v1.0 criteria after NACT were comparable in both arms with complete response in 25% patients and partial response in another 60% patients, p value 0.963.(Table 2) During NACTs, most common adverse events were; peripheral neuropathy (grade 1, 26/140), myalgia (grade 1, 38/140; grade 2; 10/140), anemia (grade 1, 24/140; grade 2 28/140) and neutropenia (grade 1, 10/140). No grade 3 adverse events were documented during NACT regimen. No patient had disease progression during NACT. Median duration of definitive treatments were 56 days (range 50 – 71 days) in radiation only arm and 59 days (range 50 – 72 days) for concurrent arm, p value 0.150. After completion of full treatment, 68.57% (48/70) patients in concurrent arm had CR against 55.72% patients (39/70) in only radiation arm, p value 0.241. Common sites for disease progression were nodal regions and pulmonary metastases. Gastrointestinal and mucositis grade 3 acute toxicities were significantly increased in concomitant chemoradiation arm. (table 3) At the end of study, 38 patients in arm A and 46 patients in arm B were eligible for response assessment. 24 patients (63.2%) in arm A were in complete response against 32 patients (69.6%) in concurrent

chemoradiation arm, p value 0.535. DFS analysis was not showing any statistical difference between the 2 arms, log rank test 0.456.(Table 4, figure 2) OS and comparisons of Quality of Life were not intentions of our study and were not calculated in our study.

REVIEW OF LITERATURE

Head and neck malignancies present at advanced stages in India. When the disease is inoperable or unresectable or patient refuses surgical management, either definitive radiotherapy or chemoradiation becomes the automatic treatment of choice. The optimum treatment for LAHNSCC is concurrent chemoradiation. The sequencing of chemotherapy and radiation still remains controversial though concomitant chemoradiation produces maximum benefit amongst all available treatments as established by meta-analyses. Neoadjuvant chemotherapy aims to reduce the initial bulk of disease with organ preservation, alleviating the symptoms and improving the quality of life. NACT provides better control of distant metastases. Brockstein *et al.* noted that in the induction chemotherapy arm (induction chemotherapy followed by split-course chemoradiotherapy), 5 year distant failure rate was 13% against 22% in split-course, hyperfractionated multiagent chemoradiotherapy, p value 0.03.[7] Advanced nodal stage was predictor of poor overall survival and increased distant recurrence. Concomitant chemoradiation has high locoregional control but ineffective in reducing distant metastases. A phase III trial comparing cisplatin-5flurouracil based induction chemotherapy with definitive radiation versus standard surgery and PORT in patients with operable pyriform sinus cancer, there was a reduction in rate of distant metastases with NACT without any improvement in overall survival.[8]. Different NACT combinations were used like cisplatin – 5fluorouracil, with or without docetaxel and paclitaxel. [9-10] Fornari *et al.* in 2002 reported complete responses of 4 (18.2%) patients in respect to primary tumour and 3 (15%) with nodal disease among 22 HNSCC patients treated with induction carboplatin (AUC = 6) and paclitaxel (200 mg/m2) for 3 cycles. Partial responses were 13(59%) and 9 (45%).[11] Dunphy *et al.* used 3 cycles of neoadjuvant chemotherapy of paclitaxel (150-265 mg/m^2) – carboplatin (AUC 7.5) combination in 62 patients of HNSCC between 1994 and 1999. The combined complete and partial response rate stood at 41 of 62 patients (66%).[12] In our study neoadjuvant CT of Paclitaxel – carboplatin produced a combined 25% complete response in both arms. Our study however does not report the subset subsite specific response rates according to the treatment groups.

The definitive treatment options for those patients responsive or non-responsive to NACT include surgery with or without PORT, definitive chemoradiation or only radiation. MACH NC provides a comprehensive analysis showcasing the benefits of addition of chemotherapy to radiation. With a median follow-up of 5.6 years, 50

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concomitant trials comprising of 9615 patients reported an absolute benefit of 6.5% at 5 years in favour of chemotherapy.[5] Updates published in 2011 showed concomitant chemoradiation benefited tumour of all subsites, with absolute benefits of 8.9% for oral cavity, 8.1% for oropharynx, 5.4% for larynx and 4% for hypopharynx.[6] Adelstein *et al.* reported concurrent cisplatin with conventional radiotherapy was producing better 3-year overall survival (37 vs 23 and 27% over radiation alone and split-course radiation, respectively; p = 0.014) but that did not translate into improved overall survival. Toxicity was increased with concurrent chemotherapy and radiation.[14] While all studies do show better prognosis with concomitant chemoradiation, the potential increased adverse events associated with chemoradiation often deter radiation oncologists from trying intensives regimens or produce inadvertent delays and non-compliance from patients. Often because of co-morbidities like uncontrolled diabetes, impaired renal functions, poor nutritional status, intensive CTRT cannot be prescribed. These were the reasons why we opted out for comparison between only definitive radiation versus standard chemoradiation arm for patients in our setup where majority of patients do not advocate use of concurrent chemoradiation inspite of counseling and adverse events often leads to increased treatment delays, poor compliance and dropouts. Our study was showing a non-statistically significant improvement in CR, 68.57% (48/70) patients in concurrent arm against 55.72% patients (39/70) in only radiation arm, p value 0.241. After a follow up of 2 years, 24 patients (63.2%) in arm A were in complete response against 32 patients (69.6%) in concurrent chemoradiation arm, p value 0.535. Xerostomia was a persistent feature in all patients.

CONCLUSION

Even though our study failed to show any statistical significant improvement in CR in favour of CTRT arm, with small simple size and follow up without OS, definitive conclusion regarding using of only radiation cannot be made for patients with fixed and bulky nodal disease and in our settings where induction chemotherapy is used extensively.

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Table 1. Patients characteristics

PATIENTS CHARACTERISTICS	GR OUP A	GROUP B	P VALUE
AGE GROUPS			
31-40 yrs	7	7	
41-50 yrs	17	18	0.997
51-60 yrs	25	24	
61-70 yrs	21	21	
GENDER			
MALES	58	59	0.819
FEMALES	12	11	
RELIGION			
HINDU	59	60	0.813
MUSLIM	11	10	
ADDICTION			
TOBACCO	46	48	0.794
TOBACCO+OTHERS	22	19	
NO ADDICTION	2	3	
PRIMARY SITE			
ORAL CAVITY	24	17	
OROPHARYNX	22	25	0.411
LARYNX + PHARYNX	23	28	
MAXILLA	1	0	
STAGE			
III	22	20	0.712
IV	48	50	

Table 2. RESPONSE ASSESSMENT			
RESPONSE	**GROUP A**	**GROUP B**	**P VALUE**
RESPONSE AFTER INDUCTION CHEMOTHERAPY IN BOTH GROUPS			
CR	17	18	0.963
PR	42	42	
SD	11	10	
RESPONSE AFTER COMPLETE TREATMENT			
CR	39	48	0.241
PR	20	16	
SD / PD	11	6	

Table 3. RTOG Acute TOXICTIES			
ORGANS	**GROUP A**	**GROUP B**	**P VALUE**
MARROW			0.294
GR 1	47	41	
GR 2	23	29	
GASTROINTESTINAL			0.039*
GR 1	38	23	
GR 2	21	26	
GR 3	11	21	
MUCOSITIS			0.002*
GR 1	30	17	
GR 2	26	34	
GR 3	14	19	

Table 4 a. Means and Medians for Survival Time (time measured in months)

GROUP	Mean				Median			
	Estimate	S.E	95% Confidence Interval		Estimate	S.E	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
A	16.696	0.900	14.933	18.459	20.000	1.667	16.733	23.267
B	18.286	0.805	16.709	19.863	20.000	0.904	18.228	21.772
Overall	17.466	0.607	16.276	18.656	20.000	0.675	18.678	21.322

Table 4 b. Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	.556	1	0.456

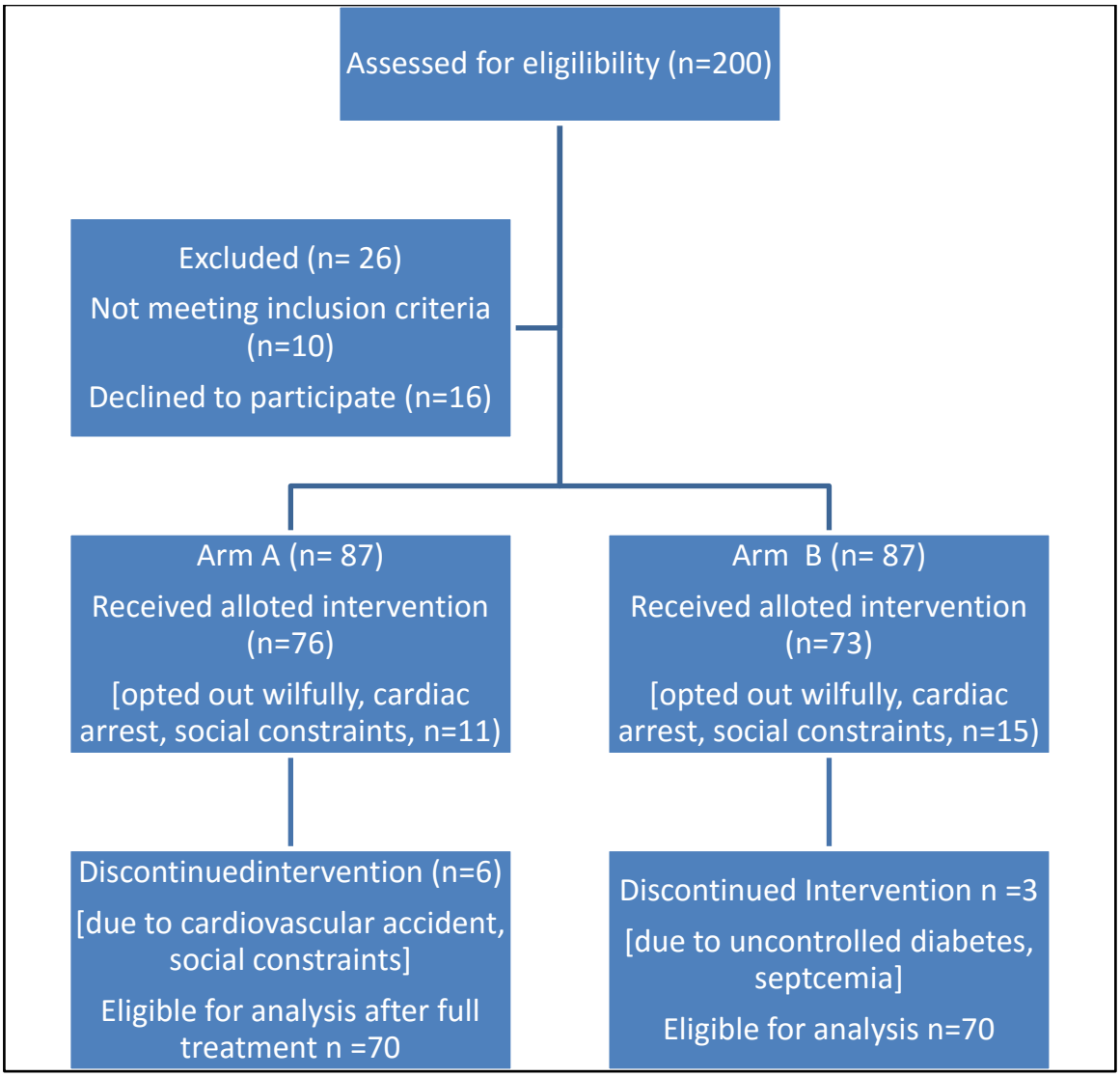

Figure 1. The treatment protocol based on CONSORT proforma for patients, till the first assessment after completion of full treatment.

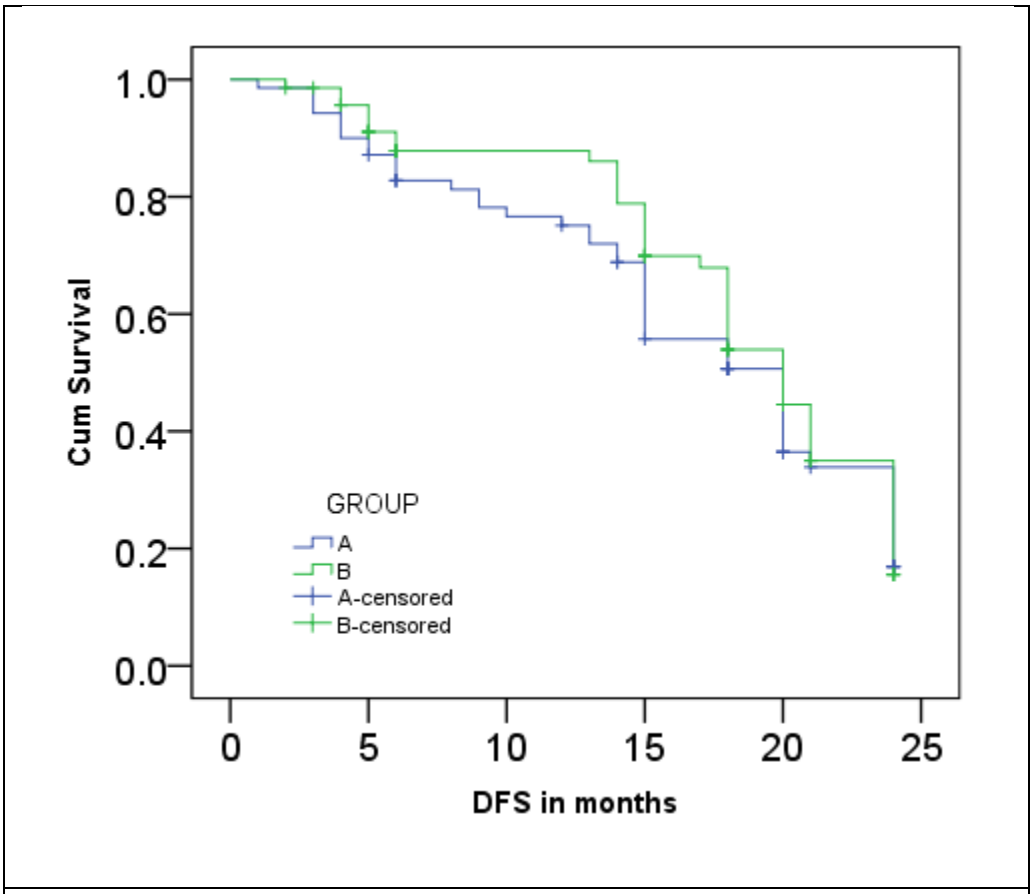

Figure 2. Disease Free Survival comparison between 2 arms, p value 0.456

Conflict Of Interest: Nil [No Author Was Associated With Any Financial Institutions / Pharmaceutical Companies For Conducting The Study.]