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COMPARATIVE STUDY OF CONCURRENT CHEMORADIOTHERAPY VS RADIOTHERAPY ALONE IN LOCALLY ADVANCED HEAD AND NECK CANCER

Dr. Saroj Dhaka[1], Dr. Neeti Sharma[2], Dr. H.S. Kumar[3], Dr. S.L. Jakhar[4], Dr. Atul Tiwari[5]
[1]Resident Doctor, Radiation Oncology Department, ATRCTRI, S.P. Medical College, Bikaner
[2]Professor and Head, Radiation Oncology Department, ATRCTRI, S.P. Medical College, Bikaner
[3]Senior Professor, Radiation Oncology Department, ATRCTRI, S.P. Medical College, Bikaner
[4]Associate professor, Radiation Oncology Department, ATRCTRI, S.P. Medical College, Bikaner
[5]Resident Doctor, Radiation Oncology Department, ATRCTRI, S.P. Medical College, Bikaner

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Corresponding author: Dr. Neeti Sharma
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Abstract
The purpose of the study was to assess difference in the treatment response and toxicity profile among two groups of unresectable locally advanced head and neck malignancies receiving concurrent chemo-radiotherapy versus radiotherapy alone after completing neoadjuvant chemotherapy.
50 patients received neoadjuvant chemotherapy (inj. paclitaxel 175 mg/m^2 D1 , Cisplatin 80mg/m^2 devided in 2 days & inj 5FU 1gm/m^2 iv d1&d2).Then randomly allotted into above two groups to receive 66 Gy fractionated RT alone versus RT along with concurrent 3 weekly inj Cisplatin 80mg/m2 devided in two days. Disease response was evaluated by RECIEST criteria.
All patients tolerated treatment well, no major adverse effects were monitored in two groups. There was no significant statistical difference in treatment response, which was found 88% vs 80% in concurrent CTRT vs RT alone .however toxicity profile was higher in concurrent CTRT group. The 6 months PFS were 83.3% and 78.3% in CTRT and RT alone groups respectively ;(x2=0.196, p value>.05)
Keywords: Radiotherapy alone, Induction chemotherapy, Unresectable locally advanced head and neck cancer.

INTRODUCTION:

The incidence of squamous cell carcinoma of the head and neck (HNSCC) is increasing, with more than 70% of cases occurring in developing world[(1)]. It is now the sixth most common malignancies, worldwide[(2)] with an annual incidence of head and neck cancers worldwide is more than 550,000 cases with around 300,000 deaths each year[(3)]. Over 200,000 new cases of head and neck cancers are registered every year in India. In our institute Acharya Tulsi Regional Cancer Training And Research Institute 3671 new head and neck cases were registered in 2016.

It is the second most common malignancy in India (most common in males while 4th most common in females).[(4)] Male to female ratio ranges from 2:1 to 4:1. About 90% of all head and neck cancers are squamous cell carcinomas (HNSCC) probably due to their higher indulgence in risk factors such as alcohol and tobacco consumption.

The median age at diagnosis is in the sixth decade of life. The prognosis of patients with locally advanced squamous cell cancer of head and neck (LASCCHN) is generally poor. In an attempt to improve local control of the tumor, investigators administered concomitantly with RT several drugs, such as cisplatin (DDP), 5-fluorouracil, mitomycin, and hydroxyurea, which are known to act as radiosensitizers (3,4)

The Concurrent chemo-radiotherapy improves survival over radiotherapy alone, generally attributed to improved locoregional control. Induction chemotherapy reduces metastases incidence.

MATERIALS AND METHODS

This was a randomised prospective study conducted at Acharya Tulsi Regional Cancer Treatment And Research Institute, Sardar Patel Medical College and associated group of hospitals, Bikaner.

The study protocol include 50 patients of histologically proven unresectable locally advanced squamous cell carcinoma of head and neck (LASCCN) of stage III-IV. Who were enrolled from April 2018 to Nov 2018. Inclusion criteria included inoperable, locally advanced, histologically proved stage III&IV squamous cell carcinoma of head and neck patients, ECOG performance status 0-2. Age 18-70 years, without any haematological, cardiac, renal or liver function abnormality, no previous history of treatment for the head and neck cancer and no any other concurrent malignancies.

All 50 patients were received three cycle of induction chemotherapy, each consisting of inj. Paclitaxel 175mg/m^2 on day1, inj Cisplatin 80mg/m^2 devided in two days and inj 5FU 1gm/m^2 on day1 &2. Inj G-CSF administration after 48 hours of TPF chemotherapy cycle was implemented in the study. Prophylactic Ciprofloxacin (500mg PO bid) was given to every patient from days 6-12 after TPF chemotherapy cycle. After 3-4 weeks from last cycle of chemotherapy patients were randomly assigned to two arms either CTRT (arm A) or EBRT alone (arm B), 25 patients in each. Patients in arm A received a total 66Gy in 33fr (2Gy per fraction), administered daily (5 days per week) for 5 weeks (conventional fractionated radiotherapy) with 3 weekly inj Cisplatin 80mg/m^2 devided in two days. Treatment volume were included primary tumor site plus neck node regions. . Parallel opposed right-left lateral fields were planned. . The dose was prescribed at midline. External beam radiotherapy was given with radiation therapy parameter on cobalt-60 machines Theratron 780E/ 780C/Bhabhatron II with photon energies of 1.25MeV. Minimum treatment distance was>=80 cm SSD. Patients in armB received EBRT alone, same as arm A without concurrent chemotherapy.

Patients were under monitoring after every course of chemotherapy and prior to & during radiotherapy. In each monitoring, patients were assessed for treatment response, control of symptoms and any treatment related morbidity by doing complete blood counts, biochemistry profile consisting of RFT & LFT, ENT examination, chest X-ray, USG Abdomen. Toxicity haematological, renal, biochemical, skin reactions and disease response were assessed. After 4-6 weeks of completion of radiotherapy patients were called for first follow up visit and were assessed for treatment response and symptoms relief. On first follow up visit complete general-physical examination, ENT examination, haemogram, RFT, RBS & CECT head and neck were done for treatment response & toxicity evaluation and metastatic workup were consist of chest X-ray, USG Abdomen and LFT.

The primary object of study was to compare the efficacy of concurrent chemotherapy over EBRT alone. Result of both arms were analysed & compared in terms of various aspects like tumor response, symptom relief and treatment related toxicities.

Results

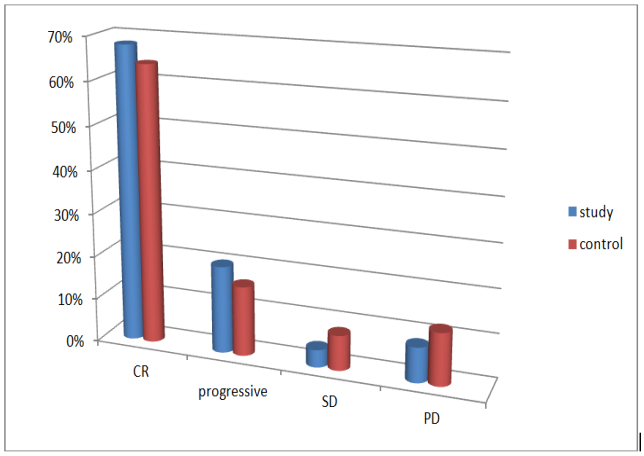
The baseline patients and tumor characteristics are shown in Table 1. No stastiscally significant difference was found in patients and tumor characteristics in both arms. The treatment Response at different follow-up visits are shown in Table 2, 3 and 4. The treatment related toxicities toxicities are shown in Table 5.

Table 1: Patients characteristics

Patients characteristics	Study Arm	Control Arm
Age (in years)		
Median age Range	56yr 38-70 yrs	56 yr 36-69 yrs
Sex		
Male Female	24 1	23 2
ECOG		
0 1 2	9 14 2	9 13 3
Tumor stage		
T2 T3 T4	1 19 5	2 18 5
Nodal stage		
N0 N1 N2 N3	6 7 12 0	12 6 5 2
Group stage		
Stage III Stage IV	11 14	15 10
Anatomical site		
Oral cavity/ Oropharynx Hypopharynx Larynx	13 8 4	17 5 3

Table 2: Treatment response at 4-6 weeks

Treatment response @ 4-6 weeks	Number of patients	
	Study arm (25) 100%	Control arm (25) 100%
Regressive disease CR PR Total (CR+PR)	 17 (68%) 5 (20%) 22 (88%)	 16 (64%) 4 (16%) 20 (80%)
Stable disease	1 (4%)	2 (8%)
Progressive disease	2(8%)	3(12%)



Graph 1:

Table 3: Treatment Response at 3 months

Treatment response @ 3 months	Number of patients	
	Study arm (23) 100%	Control arm (24) 100%
Regressive disease CR PR Total (CR+PR)	 14 (60%) 6 (26%) 20 (86%)	 13 (54.16%) 7 (29%) 20 (83.3%)
Stable disease	1 (4.3%)	1 (4.2%)
Progressive disease	2 (8.6%)	3 (12.5%)

Table 4: Treatment Response at 6 months

Treatment response @ 6 months	Number of patients	
	Study arm (22) 100%	Control arm (21) 100%
Regressive disease CR PR Total (CR+PR)	9 (40.9%) 10 (45.5%) 19 (86.4%)	8 (38.1%) 9(42.8%) 17 (80.9%)
Stable disease	1 (4.5%)	1 (4.7%)
Progressive disease	2 (9%)	3 (14.3%)

Table 5: Treatment related toxicities

Toxicities	CTRT (arm A)		RT alone (arm B)	
Hematological	**Grade 2**	**Grade 3**	**Grade 2**	**Grade 3**
Anemia	7(28%)	1(4%)	5(20%)	0(0%)
Thrombocytopenia	2(8%)	0(0%)	1(4%)	0(0%)
Neutropenia	3(12%)	2(8%)	3(12%)	1(4%)
Non Hematological				
Nausea & Vomiting	6(24%)	3(12%)	4(16%)	2(8%)
Diarrhoea	0(0%)	0(0%)	0(0%)	0(0%)
Infection	2(8%)	0(0%)	1(4%)	0(0%)
Decrease Appetite	6(24%)	2(8%)	4(16%)	2(8%)
Dysphagia	16(64%)	4(16%)	16(64%)	2(8%)
Skin Reaction	17(68%)	6(24%)	18(72%)	5(20%)
Nephropathy	0(0%)	0(0%)	0(0%)	0(0%)
Neuropathy	5(20%)	1(4%)	4(16%)	1(4%)
Stomatitis	17(68%)	8((32%)	19(76%)	6(24%)

Most of patients had ECOG performance status 1&2, median age 56 yr, male gender, median weight 51 kg & stage III & IV of locally advanced head and neck cancer in both arms. During the treatment none of the patient lost from follow up or expired in both arms. Total 25 patients were received complete treatment in each arm. Nine patients showed >5% of weight loss during study; 6(24%) and 3(12%) patients from arm A and arm B respectively.

The follow up was done at 4-6 weeks after completion of chemo -radiotherapy, 17 and 16 patients had complete response in study & control arm for any stage (X^2=.08, p>.05) ; which was insignificant. Although total 22 &20 patients had regression (x^2=0.59, p>.05), 1 & 2 patients had stable disease and 2 & 3 patients had progression of disease in study & control arm respectively. The 6 months PFS were 83.3% and 78.3% in CTRT and EBRT alone arm respectively ;(x^2=0.196, p value>.05)

There was no any grade 4 hematological & nonhematological toxicities were found in both arms. During the induction TPF hematological toxicities in terms of Anemia & Neutropenia were managable. Grade 3 neuropathy was found in 1(4%) & 1 patient (4%) in study & control arm respectively). Stomatitis and Skin reaction of grade 3 were also higher in CTRT arm. The symptoms relief was similar in both arms.

Discussion

Treatment of head and neck cancer is a multimodality approach, requiring surgery, chemotherapy and radiotherapy on the basis of the site and stage of the tumor. More than two third of head and neck cancer

patients require radiation therapy, which can be given either alone or concurrently with chemotherapy. Radiation therapy can be given either as definitive or adjuvant form, sometimes even for palliation of symptoms. According to the study by Delaney et al. radiation therapy was indicated at some point in 74% of all patients with head and neck carcinoma.

The role of induction chemotherapy before radiotherapy has been extensively investigated during the last decade. Unfortunately, it seems that there is no survival benefit from this combined modality approach with most of the patients developing locoregional recurrences. In addition, another disadvantage from the use of induction chemotherapy is that there is a considerable number of patients who refuse local therapy after the completion of induction chemotherapy and for this reason their survival may also compromised.

Different studies have shown that infection with certain strains of human papilloma virus (HPV) is linked to the development of HNSCC.HPV infection accounts for the increasing incidence of HNSCC in younger population. The prognosis of HPV positive patients is substantially better than those associated with tobacco. The prevalence of human papilloma virus (HPV) in oropharyngeal cancers is roughly 25%. HPV status, was unknown in our study and could be a confounding factor.

3 patients in CTRT arm & 4 patients in EBRT alone arm were expired during 6 month follow up ; but the deaths caused by disease itself were only two in each arm.

The expected higher proportion of febrile neutropenia during induction chemotherapy was controlled with prophylactic G-CSF, and Ciprofloxacin.

Conclusion

In conclusion, this study failed to show advantage of concurrent chemoradiotherapy over EBRT alone in terms of overall response rates and 6 months PFS in unresectable LASCCHN. Small number of patients and relatively short follow-up remains the major limitations of this study.

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