

Comparative Study of Concurrent Chemoradiotherapy vs Radiotherapy alone in Locally Advanced Head and Neck Cancer

Saroj Dhaka

Nishant Kamboj

Neeti Sharma

Rajesh Kumar Kumar

Kamlesh Kumar Harsh

Shankar Lal Jakhar

Assistant Professor, Dr S N Medical College Jodhpur, India.

Senior Resident, Atrctri, India.

Senior Resident, Atrctri, India.

Senior Resident, Atrctri, India.

Senior Resident, Atrctri, India.

Senior Resident, Atrctri, India.

Purpose: The purpose of this study was to compare 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.

Material and methods: Total 50 patients received neoadjuvant chemotherapy (inj. paclitaxel 175 mg/m² D1, Cisplatin 80mg/m² divided in 2 days & inj 5FU 1gm/m² 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 divided in two days. Disease response was evaluated by RECIST criteria.

Result: 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).

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 ATRCTRI (Acharya Tulsi Regional Cancer Treatment 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 simple randomized prospective study conducted at Acharya Tulsi Regional Cancer Treatment and Research Institute (ATRCTRI), Sardar Patel Medical College and associated group of hospitals, Bikaner, Rajasthan.

Eligibility criteria The study protocol included 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/m² on day1, inj Cisplatin 80mg/m² divided in two days and inj 5FU 1gm/m² 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/m² divided 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 control of symptoms and any treatment related morbidity by doing complete blood counts, biochemistry profile consisting of RFT & LFT, ENT examination, chest Xray, 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.

Patient characteristic	Arm A	Arm B
Age (years)	59 (39-68)	58 (41-70)
Median age, Range (years)		
Sex		
Male	44	46
Female	6	4
ECOG PS Status		
0	16	17
1	24	22
2	10	11
Tumor Stage		

T3	25	24
T4	15	16
Nodal Stage		
N0	12	10
N1	10	12
N2	23	21
N3	5	7
Group Stage		
Stage III	23	22
Stage IV	27	28
Anatomical Site		
Oral cavity	17	15
Oropharynx	13	15
Hypopharynx	12	10
larynx	8	10

Table 1. Patients’ demographic and Clinicopathologic Characteristics.

No statistically 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.

Treatment Response at 6-8 weeks	Arm A (25) 100%	Arm B (25) 100%
Regressive disease		
CR	17 (68)	16 (64)
PR	5 (20)	4 (16)
Total (CR+ PR)	22 (88)	20(80)
Stable disease	1 (4)	2 (8)
Progressive disease	2 (8)	3 (12)

Table 2. Treatment Response at 6-8 Weeks.

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

Table 3. Treatment Response at 3 Months.

Treatment response @ 6 months	Number of patients	
	Study arm (22) 100%	Control arm (21) 100%
Regressive disease	9 (40.9)	8 (38.1)
CR	10 (45.5)	9 (42.8)
PR	29 (86.4)	17 (80.9)
Total (CR+ PR)		
Stable disease	1 (4.5)	1 (4.7)
Progressive disease	2 (9)	3 (14.3)

Table 4. Treatment Response at 6 Months.

The treatment related toxicities are shown in Table 5.

Toxicities	CTRT (arm A) (%)		RT alone (arm B) (%)	
	Grade 2	Grade 3	Grade 2	Grade 3
Haematological				
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-Haematological				
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)

Table 5. Treatment Related Toxicities.

Most of patients had ECOG performance status 1 & 2, median age 56 year, 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; ($x^2 = 0.196$, $p \text{ value} > .05$). There was no any grade 4 haematological & nonhematological toxicities were found in both arms. During the induction TPF haematological toxicities in terms of Anemia & Neutropenia were manageable. 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 [5-11].

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.

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.

Acknowledgments

Statement of Transparency and Principals:

- Author declares no conflict of interest
- Study was approved by Research Ethic Committee of author affiliated Institute.
- Study's data is available upon a reasonable request.
- All authors have contributed to implementation of this research.

References

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM, Jemal A, Center MM, Ward E, Forman D, Tsujimoto H. QOL comparison of PG and TG 415. *Int J cancer*. 2010; 127:2893-917.
2. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. *Journal of the National Cancer Institute*. 1996; 88(13)[DOI](#)
3. Posner MR, Haddad RI, Wirth L, Norris CM, Goguen LA, Mahadevan A, Sullivan C, Tishler RB. Induction chemotherapy in locally advanced squamous cell cancer of the head and neck: evolution of the sequential treatment approach. *Seminars in Oncology*. 2004; 31(6)[DOI](#)
4. Ri H, Dm S. Recent advances in head and neck cancer. *The New England journal of medicine*. 2008; 359(11)[DOI](#)
5. Pignon J, Maître A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology*. 2009; 92(1)[DOI](#)
6. Brockstein B, Haraf DJ, Rademaker AW, Kies MS, Stenson KM, Rosen F, Mittal BB, et al. Patterns of failure, prognostic factors and survival in locoregionally advanced head and neck cancer treated with concomitant chemoradiotherapy: a 9-year, 337-patient, multi-institutional experience. *Annals of Oncology: Official Journal of the European Society for Medical Oncology*. 2004; 15(8)[DOI](#)
7. Argiris A. Induction chemotherapy for head and neck cancer: will history repeat



- itself?. *Journal of the National Comprehensive Cancer Network: JNCCN*. 2005; 3(3)[DOI](#)
8. Fu KK, Phillips TL, Silverberg IJ, Jacobs C, Goffinet DR, Chun C, Friedman MA, Kohler M, McWhirter K, Carter SK. Combined radiotherapy and chemotherapy with bleomycin and methotrexate for advanced inoperable head and neck cancer: update of a Northern California Oncology Group randomized trial. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 1987; 5(9)[DOI](#)
 9. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *Journal of the National Cancer Institute*. 2000; 92(3)[DOI](#)
 10. Bourhis J, Le Maître A, Baujat B, Audry H, Pignon J. Individual patients' data meta-analyses in head and neck cancer. *Current Opinion in Oncology*. 2007; 19(3)[DOI](#)
 11. Paccagnella A, Orlando A, Marchiori C, Zorat PL, Cavaniglia G, Sileni VC, Jirillo A, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. *Journal of the National Cancer Institute*. 1994; 86(4)[DOI](#)