Original Article

A comparative evaluation of neoadjuvant chemotherapy followed by concomitant chemoradiation versus accelerated radiation therapy versus conventional radiation therapy in a locally advanced head and neck carcinoma

ABSTRACT

Context: Head and neck cancers (HNCs) include malignancies of oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, paranasal sinuses, and major and minor salivary glands. Worldwide incidence of HNC cases is 4.8%, whereas in India, it is 14.3%.

Aims: Evaluation and comparison of the efficacy, tolerability, and toxicity of neoadjuvant chemotherapy (NACT) with docetaxel, carboplatin, and 5-fluorouracil (TPF) followed by concomitant chemoradiation in one group, accelerated radiation therapy (RT) in second group, and conventional RT in third group.

Subjects and Methods: The present randomized prospective study was conducted on locally advanced head and neck carcinoma patients who were randomly divided into three groups. All patients received NACT with 3-weekly TPF, for 3-courses. Group I-patients received concomitant conventional RT, 64 Gy/32 fractions/6.2-week along with three weekly carboplatin 300 mg/m^2 3-cycles. Group II-patients received accelerated RT given six fractions per week, total dose 64 Gy/32 fractions/5.2-week. Group III-patients received conventional RT, 64 Gy/32 fractions/6.2-week.

Results: The overall response rate to NACT was 100% in all groups. At last follow-up, in Group I – 52% remained alive with no evidence of disease (NED), 39% remained alive with residual disease, and 9% had locoregional recurrence. In Group II – 46% remained alive with NED, 46% remained alive with disease, 8% had locoregional recurrence, whereas in Group III – 40% remained alive with NED, 44% remained alive with disease, and 16% had locoregional recurrence.

Conclusions: NACT followed by concomitant chemoradiation is a better treatment protocol as compared to accelerated RT or conventional radiotherapy, in terms of better complete response rates with acceptable toxicity profile.

Keywords: Accelerated radiation, concomitant chemoradiation, conventional radiation, head and neck cancer, locally advanced head and neck carcinoma

INTRODUCTION

Globally, newly diagnosed head and neck cancer (HNC) cases are 686,328 annually which is 4.8% of all cancers and deaths due to HNC are 375,665 which is 4.6% of all cancers. Newly diagnosed HNC cases in India are 145,087 annually, which are 14.3% of all cancers and deaths are 105,247, which are 15.4% of all cancer deaths.[1] Malignancies of oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, paranasal sinuses, and major and minor salivary glands constitute

Garima Malik, Anil Kumar Dhull, Rajeev Atri, Vivek Kaushal

Department of Radiation Oncology, Regional Cancer Centre, Pt. B. D. Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India

Address for correspondence: Dr. Anil Kumar Dhull, Department of Radiation Oncology, Regional Cancer Centre, Pt. B. D. Sharma Post Graduate Institute of Medical Sciences, P. O. Box: 100, GPO, Rohtak - 124 001, Haryana, India.
E-mail: anilkdhull@gmail.com

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HNCs, and majority of them arise from the surface epithelium and are squamous cell carcinoma (SCC).[2] The dominant risk factors for the development of HNCs are tobacco and alcohol use.[3,4] The most important determinant of prognosis is stage at diagnosis. The 5-year survival for Stage I patients exceeds 80% but is <40% in locally advanced head and neck carcinoma (LAHNC).[5]

In general, either surgery or radiation is effective as single-modality therapy for patients with early-stage disease (Stage I or II) for most sites.[5] LAHNC are usually treated with combination therapy including surgery, radiation, and chemotherapy (CT).[5,6]

Neoadjuvant CT (NACT) is aimed at both the disseminated disease and the primary tumor. It may reduce the number of clonogenic cells and cause the reoxygenation of the surviving hypoxic cells, both of which render tumors more controllable by radiation. NACT followed by definitive radiation therapy (RT) has been studied for organ preservation in patients with locally advanced cancers of the larynx and of the hypopharynx. NACT may also be used as a method to predict tumor response to chemoradiation.[7]

Radiation may be more effective for controlling the localized primary tumor, because it can be aimed and large doses given, but it is ineffective against disseminated disease. CT, on the other hand, may be able to cope with micro-metastases, whereas it could not control the larger primary tumor.[8] In LAHNC, carboplatin and cisplatin both have been found to produce a survival benefit when added to RT. Although it appears that cisplatin may be more active, carboplatin is better tolerated.[9]

The rationale for accelerating radiation schedules is predicated on tumor cells undergoing accelerated repopulation during the treatment course after a lag time. Shortening of overall treatment time, lessen the total dose of radiation wasted in compensating for accelerated tumor cell repopulation during treatment.[10]

NACT with docetaxel, carboplatin, and 5-fluorouracil (TPF) regimen is known to decrease tumor size and improve survival in LAHNC. Following NACT, patients are usually treated by concomitant platinum-based chemoradiation which is better than conventional RT alone. However, some of the patients may develop a compromised bone marrow, after NACT, where further CT may not be possible. Accelerated RT with 6-fractions a week has shown better response rates than conventional 5-fractions a week. In light of the above factual matrix, the present study was planned to evaluate the efficacy, tolerability, and toxicity of NACT with TPF followed by concomitant chemoradiation in one group, accelerated RT in second group, and conventional RT in third group, in patients of LAHNC.

SUBJECTS AND METHODS

The present prospective, randomized, comparative, open label, parallel study was conducted on 75 previously untreated, histopathologically proven patients of SCC of head and neck. Patients included in the study were those having AJCC Stage III/IV and a positive biopsy for SCC of head and neck, Karnofsky Performance Status (KPS) >70, normal blood biochemistry, liver and kidney function test. The patients having distant metastases; prior radiation, surgery or CT for the disease; KPS <60; pregnant or lactating patient; associated medical conditions were excluded from the study.

Neoadjuvant chemotherapy

All 75 patients received NACT consisting of injection docetaxel 80 mg/m^2, injection carboplatin 300 mg/m^2, and injection 5-fluorouracil 600 mg/m^2, every 3-weekly × 3-courses (total period 6-week).

Group I

It comprised 25 randomly selected patients who received NACT as mentioned above followed by concomitant conventional radical RT, given five fractions per week, in total dose of 64 Gy/32 fractions/6.2 weeks (i.e. 2 Gy/fraction) along with 3 weekly carboplatin 300 mg/m^2 × 3-cycles.

Group II

It comprised 25 randomly selected patients who received NACT as mentioned above followed by accelerated radical RT given six fractions per week, in a total dose of 64 Gy/32 fractions/5.2 weeks (i.e., 2 Gy/fraction).

Group III

It comprised 25 randomly selected patients having histopathologically proven squamous cell carcinomas of the head and neck who received NACT as mentioned above followed by conventional radical RT given five fractions per week, total dose 64 Gy/32 fractions/6.2 weeks (i.e. 2 Gy/fraction).

Radiotherapy technique

Radiotherapy was delivered in supine position by parallel opposing fields including the primary tumor, disease extension, and neck nodes. The shrinking field technique was used to spare the spinal cord after a dose of 44 Gy.

RESULTS

Patient characteristics

Mean age at presentation in Group I, II, and III was 53-, 54-, and 56-year respectively. Overall, 92% patients were males, remaining 8% were females. Total male to female ratio was 11.5:1. Overall, 91% patients were from rural areas, whereas 9% patients belonged to urban background.

In this study, overall 95% patients were smokers (all more than 5-year history of smoking), whereas 5% patients were those who never smoked. Out of the total enrolled patients in all the groups, 68% were alcoholic. Total patients with KPS 80 were 13% and KPS 90 were 87%. Throat pain was the most common chief complaint with 41% patients followed by difficulty in swallowing in 31% patients [Table 1].

Tumor characteristics

Oropharynx was most common primary International Classification of Diseases (ICD) site observed in 77% cases. Base of tongue was the most common primary ICD site in Group I (48%) and Group III (48%), whereas tonsil is the most common primary ICD site in Group II (32%). According to the AJCC 2010 staging system, maximum patient were of T3 in Group I (76%), Group II (64%), and Group III (84%). N2 was the most common nodal status at presentation in Group I (36%) and Group II (44%), whereas N1 and N2 were equally present in Group III (36%). No status was seen in 7 patients (28%) in all groups. Stage III patients were of maximum number in Group I (52%) and Group III (60%), but in Group II maximum patients belonged to Stage IV (64%). The difference was not significant statistically and is attributable to randomization. Ulceroproliferative tumor (77%) was found to be the most common type; indurated tumors were only 23% of all tumors. This study revealed that the most common histopathological subtype was moderately differentiated SCC being 78% in all groups followed by SCC (not otherwise specified): 15%; followed by poorly differentiated SCC being 7% [Table 2].

Hematological toxicity during neoadjuvant chemotherapy

Hematological toxicity was assessed each time before NACT as per the WHO criteria. Hemoglobin (Hb) was reduced in 13 out of 75 patients (17%) after 1st NACT and in 16 out of 75 patients (21%) after 2nd NACT. Only one patient in Group I (chemoradiotherapy) had Grade III anemia (Hb = 7.6 g%) after 2nd NACT, hence decided to omit further course of NACT. There was no Grade IV anemia in any group at any time. During 3rd NACT, Grade III neutropenia was seen in 40% patients in Group II, whereas in Group I and II, it was seen in 8% and 12% patients, respectively. During 2nd NACT, Grade III neutropenia was seen in 8%, 20%, and 4% in Groups I, II, and III, respectively. During 1st NACT, Grade III neutropenia was seen only in Group I (4%) and Group II (8%). During 3rd NACT, Grade III thrombocytopenia was seen in 42% patients in Group I, 28% patients in Group II and 36% patients in

Table 1: Patient characteristics

Patient characteristics	Group I (*n*=25) Concomitant RT (%)	Group II (*n*=25) Accelerated RT (%)	Group III (*n*=25) Conventional RT (%)	*P*
Age group (years)				
≤50	40	48	36	0.734
>50	60	52	64	
Gender				
Male	96	92	88	0.581
Female	4	8	12	
Background				
Rural	88	96	88	0.532
Urban	12	4	12	
Smoking				
Smoker	96	96	92	0.768
Nonsmoker	4	4	8	
KPS				
80	8	20	12	0.446
90	92	80	88	
Symptoms				
Dysphagia	44	24	24	0.758
Neck mass	16	16	16	
Breathlessness	0	0	4	
Nonhealing ulcer	0	4	4	
Hoarseness	12	8	4	
Throat pain	28	48	48	

RT - Radiotherapy; KPS - Karnofsky performance status

Table 2: Tumor characteristics

Tumor characteristics	Group I (*n*=25) Concomitant RT (%)	Group II (*n*=25) Accelerated RT (%)	Group III (*n*=25) Conventional RT (%)	*P*
Morphology				
Ulceroproliferative	68	80	84	0.372
Indurated	32	20	16	
Histopathology				
WDSCC	0	0	0	0.884
MDSCC	76	80	80	
PDSCC	4	8	8	
SCC (NOS)	20	12	12	
Site of tumor				
Oral cavity	0	12	0	0.078
Oropharynx	68	80	84	
Hypopharynx	12	0	4	
Larynx	20	8	12	
Stage-wise distribution				
III	52	36	60	0.225
IV	48	64	40	

RT - Radiotherapy; MDSCC - Moderately differentiated squamous cell carcinoma; WDSCC - Well differentiated squamous cell carcinoma; PDSCC - Poorly differentiated squamous cell carcinoma; SCC - Squamous cell carcinoma; NOS - Not otherwise specified

Group III. There was only one patient of Group III, who had Grade IV thrombocytopenia. Hence, overall the compliance to NACT with TPF was good.

Response rates postneoadjuvant chemotherapy

Overall 100% response rate was seen in all groups, to three cycles of NACT. Complete response after three NACT was seen in 12% patients in Group I, 20% patients in Group II, and 12% patients in Group III, $P = 0.653$ (not significant) [Table 3].

Hematological toxicity during concomitant chemotherapy

Hematological toxicity was assessed each time before three cycles of concomitant CT given in Group I of study. There was no Grade III anemia seen in any group at any time during concomitant CT. Grade III neutropenia was seen in 74% patients and Grade III thrombocytopenia was seen in 56% patients during concomitant CT. Two patients received only one cycle of concomitant CT.

Acute radiation reactions observed during radiotherapy

Radiation reactions in all patients were noted during and after radiation treatment completion and were graded as per the Radiation Therapy Oncology Group (RTOG) grades. Grade III skin reaction was seen in 21% patients in Group II, 17% in Group I and only 4% patients in Group III at completion of radiotherapy ($P = 0.197$). None of the patients developed Grade IV skin reactions. RTOG Grade III mucositis observed at end of treatment was seen in 33% patients in Group II, 22% patients in Group I, and 4% patients in Group III ($P = 0.033$ statistically significant). Grade IV mucosal reactions were not seen in any of the patients.

Patients completing intended treatment

Two patients (8%) in Group I (concomitant RT) did not complete the intended treatment and left after 13# and 9# of RT getting only 26 Gy and 18 Gy respectively out of intended 64 Gy, due to nontolerability of concomitant chemoradiation as they developed severe nausea and vomiting after the 1st cycle of concomitant chemotherapy (CCT). One patient (4%) in Group II (accelerated RT) left the treatment after getting 8 Gy (4#) due to Grade III mucositis.

Disease status at 1 month follow-up

Locoregional control and disease status at 1 month follow-up was assessed in all patients [Table 4]. Complete tumor response was seen in 16 (69%) patients in Group I, 14 (59%) patients in group in II, and 15 (60%) patients in Group III, at 1st month of follow-up, $P = 0.693$ (not significant). Complete nodal response was seen in 11 (65%) patients in Group I, 10 (59%) patients in Group II, and 10 (56%) patient in Group III at 1 month of follow-up, $P = 0.849$ (not significant). Overall complete response was seen in 15 (65%) patients in Group I, 13 (54%) patients in Group II, and 13 (52%) patient in Group III at 1 month of follow-up, $P = 0.617$ (not significant).

Table 3: Response rates post-neoadjuvant chemotherapy

Response rates (%)	Group I ($n=25$)	Group II ($n=25$)	Group III ($n=25$)
CR	12	20	12
PR	88	80	88
Overall	100	100	100

CR - Complete response; PR - Partial response

Table 4: Disease status at 1 month follow-up

Groups	Stage	Total patients	Disease status (%)	
			CR	PR
Group I	III	11*	26	22
	IV	12	39	13
	All stages	23*	65	35
Group II	III	9	16	21
	IV	15**	38	25
	All stages	24**	54	46
Group III	III	15	36	24
	IV	10	16	24
	All stages	25	52	48

*Two patients left treatment in Group I; **One patient left treatment in Group II. CR - Complete response; PR - Partial response

Disease status at last follow-up

Complete tumor response was seen in 15 (65%) patients in Group I, 13 (54%) patients in Group III, and 13 (52%) patients in Group III at last follow-up, $P = 0.617$ (not significant). Complete nodal response was seen in 10 (59%) patients in Group I and II and 9 (47%) patients in Group III at last follow-up, $P = 0.858$ (not significant). For all stages, no evidence of disease (NED), in Group I, II, and III, respectively, was 52% (12/23), 46% (11/24), and 40% (10/25). For all stages, residual disease was seen in 39% (9/23) of patients in Group I, 46% (11/24) patients in Group II, and 44% (11/25) patients in Group III. Recurrence was seen in 9% patients in Group I, 8% patients in Group II, whereas it was seen in 16% patients in Group III, $P = 0.699$ (not significant) [Table 5].

Late radiation reactions

Worst grade late subcutaneous toxicity (Grade II) was seen in 26% patients in Group I, 17% patients in Group II, and 8% patients in Group III. Worst grade late mucosal toxicity (Grade II) was seen only in Group I in 9% patients. Worst grade late salivary gland toxicity (Grade II) was seen in 13% patients in Group I, 13% patients in Group II, and 8% patients in Group III.

Disease free survival

Disease free survival (DFS) for all stages was 12/23 (52%) in Group I, 11/24 (46%) in Group II, and 10/25 (40%) in Group III, $P = 0.699$ (not significant) [Table 6].

DISCUSSION

The main objective of the study was to evaluate and compare the efficacy, tolerability, and toxicity of NACT with TPF followed by concomitant chemoradiation and their comparison with other two groups. Accordingly, we have explored the International Medical Literature and compared the results of our study to conclude the feasibility of the present study.

Majority of head and neck malignant neoplasms arise from the surface epithelium and are SCC or one of its variants, such as lymphoepithelioma, spindle cell carcinoma, verrucous carcinoma, and undifferentiated carcinoma.[11] People who use tobacco (including cigarettes, cigars, pipes, etc.,) or drink alcohol excessively are at much greater risk for developing HNCs.[3,4] Approximately, 70–80% of these patients are diagnosed with locally advanced disease and 30–50% with lymph node involvement.[12] Stage at diagnosis is the single most important determinant of prognosis. The 5-year survival for Stage I patients exceeds 80% but is <40% in LAHNC. NACT with TPF is better than PF only schedule in LAHNC; hence, we used this schedule in our study. Various famous trials are in support of this like Posner *et al*., conducted a randomized phase III trial for the treatment of head and neck SCC to compare induction CT with TPF with PF, followed by chemoradiation. There was a better locoregional control in the TPF group, but the incidence of distant metastases in the two groups did not differ significantly. Rates of neutropenia and febrile neutropenia were higher in the TPF group; CT was more frequently delayed because of hematologic adverse events in the PF group.[13] Similarly, in a phase II comparative study of TPF versus PF as induction CT in 358-patients of LAHNC. At a median follow-up of 32.5 months, the median progression-free survival (PFS) was 11.0 months in the TPF group and 8.2 months in the PF group. Treatment with TPF resulted in a reduction in the risk of death of 27%, with a median overall survival (OS) of 18.8 months, as compared with 14.5 months in the PF group.[14]

In a further study, the effectiveness of induction CT with TPF followed by radiation was compared with that of concurrent chemoradiation with TPF in LAHNC patients and concluded that the effectiveness of concurrent chemoradiation with TPF was better than that of induction CT with TPF followed by radiation.[15]

Haddad *et al*. conducted a series of four Phase I-II trials of high-dose and intermediate-dose TPF-based induction CT on 101 LAHNC patients. After a median follow-up of 49 months, 64% remain alive with NED, and 3 patients remain alive with disease, for an OS rate of 67%. Twenty-six patients had locoregional recurrences, and 5 patients had both LRR and distant metastasis. Out of 84 patients, 55 patients remain alive with NED (65%). Notably, 43 of 84 patients (51%) had oropharyngeal primary tumors, and 30 of those patients remain alive with NED (70%). Significant morbidity was low, with two treatment-related deaths. These data suggest that docetaxel adds incrementally to the efficacy of cisplatin and fluorouracil.[16]

The importance of even small amount of acceleration was emphasized by the results from the Danish Head and

Table 5: Disease status at last follow-up

Group	Stage	Total number of patients	Disease status (%)		
			NED	RD	REC
Group I (*n*=23)*	III	11*	22	22	4
	IV	12	30	17	4
	All stages	23*	52	39	9
Group II (*n*=24)*	III	9	17	21	0
	IV	15**	29	25	8
	All stages	24**	46	46	8
Group III (*n*=25)	III	15	28	24	8
	IV	10	12	20	8
	All stages	25	40	44	16
Total in all groups		72	46	43	11

*Two patients left treatment in Group I; **One patient left treatment in Group II. NED - No evidence of disease; RD - Residual disease; REC – Recurrence; NED - No evidence of disease

Table 6: Disease free survival

Disease free survival/status	Group I (concomitant chemoradiation)		Group II (accelerated RT)		Group III (conventional RT)	
	Stage III (*n*=11)	Stage IV (*n*=12)	Stage III (*n*=9)	Stage IV (*n*=15)	Stage III (*n*=15)	Stage IV (*n*=10)
Locoregional failure	5	4	5	6	6	5
Distant metastasis	0	0	0	0	0	0
Local recurrence	1	1	0	2	2	2
Locoregional control (stage wise)	5/11	7/12	4/9	7/15	7/15	3/10
Locoregional control (all stages)	12/23		11/24		10/25	
Disease free survival	12/23* (52%)		11/24** (46%)		10/25 (40%)	

*Two patients left treatment in Group I; **One patient left treatment in Group II. RT - Radiotherapy

Neck Cancer Study Group 6 and 7 trial. In the Danish trial, Overgaard *et al*. aimed to find out whether shortening of treatment time by the use of six instead of five radiotherapy fractions per week improves the tumor response in SCC. Overall 5-year locoregional control rates improved (70% vs. 60%; $P = 0.0005$). The benefit of shortening treatment time was seen for primary tumor control (76% vs. 64%; $P = 0.0001$), but not for neck-node control. Acceleration from 7 to 6 weeks improved voice preservation in laryngeal cancer (80% vs. 68%; $P = 0.007$) and improved disease-specific survival (73% vs. 66%; $P = 0.01$) but not OS. Acute morbidity was significantly more frequent with six than with five fractions, but was transient.[17]

Bourhis *et al*. did an analysis of two randomized trials of the French Head and Neck Cancer Group to compare concomitant chemoradiation and accelerated radiotherapy comparing conventional RT (70 Gy in 35 fractions) either with concomitant RT-CT (70 Gy in 35 fractions with three cycles of a 4-day regimen comprising carboplatin and 5-fluorouracil) or with very accelerated RT delivering 64 Gy in 3 weeks. The 5-year OS, specific DFS, and local-regional control rates were improved in favor of simultaneous RT-CT, whereas local-regional control was significantly improved with accelerated RT, along with a marginal effect on OS and DFS. They concluded that both concomitant chemoradiation and accelerated RT improved tumor control rates, as compared to conventional RT, along with increased but manageable toxicity.[18] In a further Phase III randomized trial on LAHNC with an Eastern Cooperative Oncology Group performance status of 0–2, accelerated radiotherapy- CT offered no PFS benefit compared with conventional chemoradiation or very accelerated radiotherapy; conventional chemoradiation improved PFS compared with very accelerated radiotherapy. Three-year PFS was 37·6% after conventional chemoradiation, 34·1% after accelerated radiotherapy-CT, and 32·2% after very accelerated radiotherapy. They concluded that CT has a substantial treatment effect given concomitantly with radiotherapy and acceleration of radiotherapy cannot compensate for the absence of CT.[19]

CONCLUSION

The present study was a feasibility study and have shown better complete response in Group II (Accelerated RT) than group III but was associated with severe acute radiation toxicity especially mucosal which was statistically significant too. Group III (Conventional RT) treatment schedule was tolerated by all the patients without significant problems however it yielded the least local control out of the three groups. Group I (Concomitant chemoradiation) showed better complete response than other two groups with toxicity profile more acceptable than group II. It is concluded that following neoadjuvant chemotherapy, concomitant chemoradiation is better schedule as compared to accelerated radiation therapy or conventional radiotherapy.

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Conflicts of interest

There are no conflicts of interest.

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