International Journal of Research in Medical Sciences
Swer D et al. Int J Res Med Sci. 2025 Jul;13(7):2855-2865
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20252019

Original Research Article

A comparative study on tumour response and treatment toxicities of two cycles versus three cycles of induction chemotherapy followed by concurrent chemoradiotherapy in the management of locoregional advanced head and neck cancer

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Received: 28 April 2025
Revised: 06 June 2025
Accepted:10 June 2025

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ABSTRACT

Background: Locally advanced head and neck squamous cell carcinoma (LA-HNSCC) is being treated by multimodality approached, the rationale of using induction chemotherapy (ICT) is to shrink the tumors, enhance local control, and improved response, supporting the use of multiple ICT cycles. This study, compares two different courses of ICT followed by concurrent chemoradiotherapy to see the improvement in tumour response and treatment toxicities.
Methods: A randomized controlled trial conducted at the department of radiation oncology, RIMS, Imphal, from July 2022 to June 2024 after approval was obtained from institutional research ethics board (REB) with a total of 61 patients, where 31 patients recruited in arm-A and 30 patients in arm-B which compares two cycles versus three cycles of ICT followed by chemo-radiotherapy. Tumor response and toxicities were assessed using RTOG and RECIST criteria.
Results: Toxicities like oral mucositis, anemia, neutropenia, thrombocytopenia were seen more in arm B as compared to arm A and KFT toxicities were higher in arm A. Late toxicities like dermatitis, xerostomia, subcutaneous fibrosis were observed higher in arm-B. Partial response (PR) was observed better in arm B but progressive disease (PD) and stable disease (SD) were higher in arm A.
Conclusions: Arm B showed slightly better tumor shrinkage but had more side effects with mucositis, nausea, and blood-related issues. Late toxicities were slightly higher in arm B. However, these differences were not statistically significant. Overall, both arms showed similar effectiveness. More research is needed to find the ideal number of ICT cycles that maximize response and minimize side effects.

Keywords: Locally advanced head and neck cancer, Induction chemotherapy, Concurrent chemoradiotherapy

INTRODUCTION

Head and neck cancers (HNCs) refers to the various neoplasms arising from different atomic subsites that included cancers of the oral cavity, pharynx, larynx, salivary glands, nose, paranasal sinuses, skull base etc.[1] HNCs is the seventh most common cancer globally, accounting for more than 660,000 new cases and 325,000 deaths annually (GLOBOCAN 2020).[2,3] Males are affected more than female with a ratio ranging from 2:1 to 4:1. Oral cavity and laryngeal cancers are the most common HNCs globally.[4] As per the departmental registry maintained by department of radiation oncology, regional institute of medical sciences, Imphal, HNCs contributed about 15.6 % of the total patients registered in the last 2 years.

Tobacco smoking, alcohol drinking, oral tobacco uses, betel and areca nut chewing are major risk factors accounting for 72% of cases when used in combination.[5] Infection with high-risk human papilloma virus 16, 18 primarily HPV-16 and Epstein Barr virus.[6] The life of patients with head and neck cancer gets entangled in numerous physical and psychological symptoms. Pain in the oral cavity and dysphagia, airway obstruction, chocking, fungating wounds, mucosal inflammation, loss of appetite, nausea and vomiting are the alarming symptoms of HNCs.[7]

In early stage, these cancers are often curable with single modality treatment with surgery or radiotherapy. In other hand, locally advanced HNCs is being increasingly treated by multimodality approaches combining surgery, radiotherapy, chemotherapy and targeted therapies.[8] The management of HNCs is directly altered by the presence or absence of metastatic cervical adenopathy.[9] Over the last decade, several approaches to improve chemo-radiotherapy outcomes in this population have achieved some progress. These efforts have included modifying treatment sequencing, chemotherapy dosing, content, and schedule and modifying radiotherapy dosing and fractionation.[10] As part of the primary treatment, systemic chemotherapy can be administered before as ICT, or during radiotherapy as concomitant chemotherapy.

The rationale of utilization of ICT in the treatment of HNCs is that the drug delivery to primary tumours with an intact vascularity is preferable to utilize the same drugs in tumours that were previously operated or irradiated, better tolerance of chemotherapy in previously untreated patients with good performance would improve the efficacy of the drugs and the possibility that subclinical metastases could be eradicated with the ICT which supports the use of more number of ICT.[11]

A combination of cisplatin and 5-fluorouracil (5-FU), every three weeks is the most commonly used regimen for induction treatment. Single-agent cisplatin is cytotoxic agent of choice for concomitant chemoradiotherapy.[12] However, the optimal number of cycles required is not known. There are very few studies comparing the two cycles of ICT with a higher number of cycles.[13]

In this study we have taken two different course of ICT regime with cisplatin 75 mg/ sq. m in divided dose for 2 days and 5-FU 1000 mg/sq. m for 3 days followed by concurrent chemo-radiotherapy (CTRT). We have taken up this study to compare 2 cycles versus 3 cycles of ICT to see the feasibility of improvement in tumour response rate and the treatment toxicities between the two proposed treatment regimens as compared to the published literatures evidence.

METHODS

A randomized controlled trial was conducted at the department of radiation oncology, regional institute of medical sciences, Imphal, Manipur, India from July 2022 to June 2024 with prior approval from institutional research ethics board (REB). The total sample size sample was 61, in which patients were allocated into arm-A and arm-B using simple randomization method.

Inclusion criteria

The study population includes patients with histopathological confirmed LA-HNSCC, stage III, IVA and IVB, age >30 years and <70 years, with Karnofsky performance status (KPS) ≥70% and with normal blood parameters and audiometry.

Exclusion criteria

Patients with nasopharyngeal carcinoma, paranasal sinus carcinoma, thyroid malignancies, previously treated LA-HNSCC with radiation therapy/chemotherapy and/or surgery, patient having second malignancy, distant metastasis, associated co-morbid medical condition, psychosis, pregnant and lactating women and patients unwilling to give consent were excluded.

In arm A patients were treated with 2 cycles of ICT with 21 days interval with cisplatin 75 mg/sq. m in two divided doses in day 1 and 2 and 5-flurouracil (5-FU) 1000 mg/sq. m from day 1-3 whereas in arm B patients were treated with 3 cycles of ICT at 3 weekly intervals with Cisplatin 75 mg/sq. m in two divided doses in day 1 and 2 and 5-FU 1000 mg/sq. m from day 1-3. Patients received standard hydration prior and during chemotherapy with prophylactic steroid and antiemetics premedication, mannitol infusion and prophylactic potassium and magnesium chloride infusion for cisplatin therapy were given. After 3 weeks of completion of chemotherapy and bone marrow recovery these patients were treated with external beam radiotherapy (EBRT) to a total dose of 70 Gray (Gy) in 35 fractions, 5 days a week for 7 weeks using shrinking field technique after spinal cord tolerance dose of 44 Gy in 22 fractions along with concurrent cisplatin 40 mg/sq. m once weekly till the completion of radiotherapy.

Acute toxicities were assessed weekly during ICT and CTRT and graded according to the RTOG acute toxicity grading. Late toxicity was assessed 3 months after completion of treatment and thereafter every 3 months till 1 year using RTOG late morbidity grading.[14] Treatment response and late response were assessed at the end of the study using RECIST criteria.[15]

Descriptive data like age, KPS analysis using mean, median and categorical variables like gender, primary site, staging, histology, treatment response and toxicity profile was be presented in terms of percentages and proportions as frequency tables and treatment response and toxicity was compared between the arms by Chi-square or fisher' exact test using SPSS-version 26 for windows (IBM Corp, Armonk, NY, USA) was used for statistical analysis.

RESULTS

A total of 61 confirmed cases were recruited, with 31 patients in arm A and 30 patients in arm B, 3 patients drop-out due to poor general condition and non-compliance. These patients withdrew from the study before the start of the treatment. All these defaulters were excluded from analysis and evaluation and hence data assessment for treatment toxicities and tumour response was done for 58 patients. In arm A, 30 patients were treated with 2 cycles of ICT and in arm B, 28 patients were treated with 3 cycles of ICT followed by CTRT. During the course of ICT treatment hospital admission was required for all patients, with proper hydration and pre medications were given. All patients showing side effect were managed accordingly with best supportive care.

Table 1 shows the pre-treatment demographic profiles of the patients in both the arms. It was observed that males were more predominant than female patients in both arms with total of 43 males (70.49%) and 18 females (29.51%). More than 59.10% of the patients were above the age of 50 years in both the arms with a mean age of 60 years. Tobacco chewing, alcohol consumption and betel nut chewing were common risk factors among most of the patients in both arms. Patients with KPS 70% to 90% were recruited among both arms with KPS 80% being the maximum number of patients.

Table 2 shows the comparison of tumour characteristics in both the arms. It was observed that the commonest site in both arms was oral cavity (36.06%) followed by larynx (24.59%), hypopharynx (22.95%) and oropharynx (16.40%), with the most common stage group was IVA (39.35%), followed by stage IVB (36.06%) and stage III (24.59%) in both arms. According to histology grade most common moderately differentiated (31.14%) followed by poorly differentiated (24.59%), undifferentiated (24.59%) and well differentiated (18.03%).

Figure 1 shows the dropout rates and reasons for dropout among the patients in both the arms. There were 3 dropout patients from this study. In arm A, there is 1 (33.33%) patient due to poor general condition while in arm B, 1 patient dropped out due to poor general condition and 1 patient dropped out due to non-compliance.

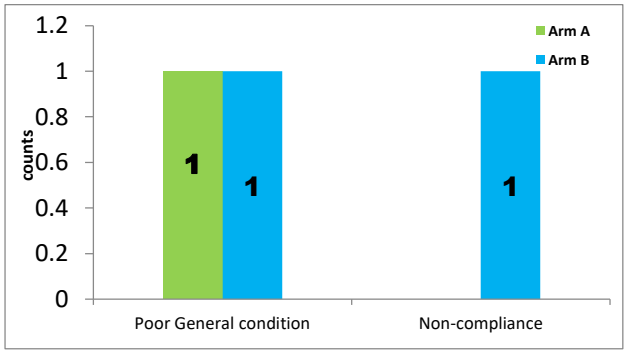

Figure 1: Dropout reasons in arm A and arm B.

Table 3 shows the acute treatment toxicities in both the arms during the ICT with two cycles of chemotherapy in arm A versus three cycles of ICT in arm B. Each toxicity was assessed weekly from the start of the ICT treatment.

Table 4 shows acute treatment toxicities observed during concurrent chemo-radiation treatment (CTRT) between both arms after post ICT. Each toxicity assessed weekly using RTOG grading from start of CTRT till end of treatment with cumulative p analysed between both arms.

Table 5 shows the late treatment toxicities after the completion of treatment in both the Arms which was observed during the follow up at 3rd month, 6th month and 9th month after the treatment. Radiation dermatitis was assessed at 3 months (M3), 6 months (M6), 9 months (M9), post-treatment with patients showing grade I and II post treatment dermatitis seen in both arms with p=0.28 at M3, and 0.56 at M6. Oral mucositis, were also assessed at M3, M6, and M9 post-treatment with grade I and II were seen in M3, M6, M9 and grade III observed at the end of M3 with 2 patients (6.66%) in arm A and 3 patients (10.71%) in arm B. Statistical analysis was done showing p-value for M3, M6, M9 at 0.09, 0.28 and 0.57 respectively. Post treatment xerostomia was also seen with grade I and II in both arms at M3, M6, M9 with p=38, 0.46 and 0.48 respectively. Subcutaneous fibrosis was also assessed post-treatment with grade I and II seen at M3, M6, M9 and grade III fibrosis seen at M9 with 10% in arm A and 10.71% in arm B. Statistical analysis was done with p=0.46, 0.29 and 0.67 in M3, M6, M9 respectively. Overall, the analysis of late treatment toxicities shows that both arms exhibited similar patterns in the incidence and severity of late toxicities, but with no significant differences between both the arms. This suggests that the treatment impact on late toxicities was comparable for both groups during the follow-up period.

Figure 2 shows treatment response at end of treatment in both arms. In arm A, 2 patients (6.66%) achieved a complete response (CR), 15 patients (50%) achieved a PR, 8 patients (26.66%) with SD, and 5 patients (16.66%) experienced PD. Whereas, in arm B, 3 patients (10.71%) achieved a CR, 18 patients (64.2%) achieved a PR, 4 patients (14.20%) with SD and 3 patients (10.71%) experienced PD with a p=0.10 showing no statistically difference between the arms.

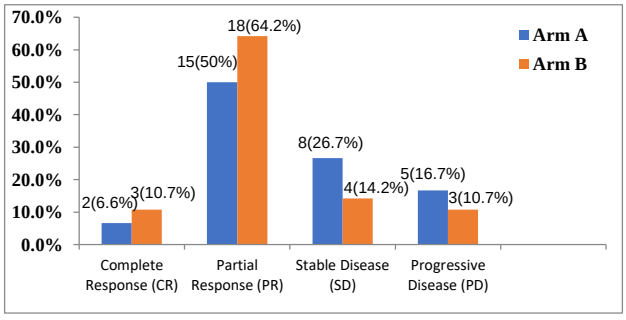

Figure 2: Tumour response at end of treatment.

In Figure 3 patients receiving ICT in radiation oncology ward at our institute. In Figure 4 RTOG grade I skin reaction at the end of 4th week during concurrent chemoradiotherapy and RTOG grade II oral mucositis observed at the end of 6th week during concurrent chemoradiotherapy.

Figure 3: Patients receiving induction chemotherapy in our institute.

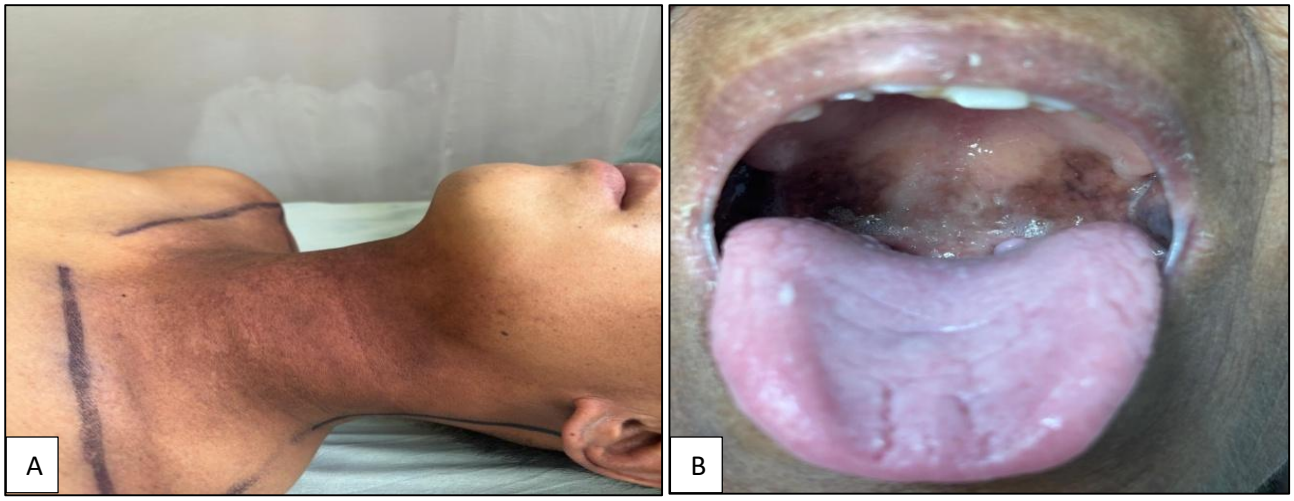

Figure 4 (A and B): RTOG grade I skin reaction at the end of 4th week during concurrent chemoradiotherapy and RTOG grade II oral mucositis observed at the end of 6th week during concurrent chemoradiotherapy.

Table 1: Pre-treatment patient profile in both the arms (n=61).

Variables		Arm-A, (n=31)	Arm-B, (n=30)
Gender	Male	19 (61.3%)	24 (80%)
	Female	12 (38.7%)	6 (20%)
	Total	31	30
Age (in years)	<50	12 (38.7%)	13 (43.3%)
	51-60	10 (32.2%)	9 (30%)
	61-70	9 (29%)	8 (26.6%)
	Mean	60	
	Total	31	30

Continued.

Variables	Arm-A, (n=31)	Arm-B, (n=30)	Variables
Risk factor	Tobacco consumption	4 (12.9%)	3 (10%)
	Alcohol	2 (6.5%)	3 (10%)
	Betelnut chewing	3 (9.7%)	1 (3.3%)
	Tobacco+alcohol	8 (25.8%)	10 (3.3%)
	Tobacco+alcohol + betelnut	10 (32.3%)	10 (3.3%)
	No bad habits	4 (12.9%)	3 (10%)
	Total	31	30
KPS	70%	10 (32.2%)	9 (30%)
	80%	16 (51.6%)	15 (50%)
	90%	5 (16.1%)	6 (20%)
	Mean	80%	
	Total	31	30

Table 2: Tumour characteristics distribution in both the arms (n=61).

Variables		Arm A, (n=31)	Arm B, (n=30)	Total, (n=61)
Primary site	Larynx	7 (22.58%)	8 (26.66%)	15 (24.59%)
	Hypopharynx	8 (25.80%)	6 (20.00%)	14 (22.95%)
	Oral cavity	12 (38.70%)	10 (40.00%)	22 (36.06%)
	Oropharynx	4 (12.90%)	6 (20.00%)	10 (16.40%)
	Total	31	30	61
T stage	T1	1 (3.22%)	1 (3.33%)	2 (3.27%)
	T2	6 (19.40%)	6 (20.00%)	12 (19.67%)
	T3	16 (51.60%)	15 (50.00%)	31 (50.82%)
	T4	8 (25.80%)	8 (26.70%)	16 (26.24%)
	Total	31	30	61
N stage	N0	-	-	-
	N1	6 (19.35%)	8 (26.70%)	14 (21.32%)
	N2	19 (59.30%)	17 (56.70%)	36 (59.02%)
	N3	6 (19.40%)	5 (16.70%)	11 (18.03%)
	Total	31	30	61
Stage grouping	III	8 (25.80%)	7 (21.85%)	15 (24.59%)
	IVA	13 (41.90%)	11 (34.37%)	24 (39.35%)
	IVB	10 (32.25%)	12 (37.55%)	22 (36.06%)
	Total	31	30	61
Histology grade	Well differentiated	5 (16.10%)	6 (20.00%)	11 (18.03%)
	Moderately differentiated	11 (35.40%)	9 (30.00%)	20 (32.78%)
	Poorly differentiated	8 (25.80%)	7 (23.33%)	15 (24.59%)
	Un-differentiated	7 (22.50%)	8 (26.66%)	15 (24.59%)
	Total	31	30	61

Table 3: Acute treatment toxicities in both the two arms during induction chemotherapy (n=58).

Durations	Grade	Arm A, (n=30)	Arm B, (n=28)	P value
Oral mucositis				
Week 1-4	I-II	-	-	-
Week 5	I	6 (20.00%)	9 (32.14%)	0.28
	II	5 (16.66%)	6 (21.40%)	
Week 6	I	6 (20.00%)	7 (25.00%)	0.71
Week 7	I	-	5 (17.80%)	-
Week 8	I	-	4 (14.80%)	-
Week 9	I	-	2 (7.10%)	-

Continued.

Durations	Grade	Arm A, (n=30)	Arm B, (n=28)	P value
Anemia				
Week 1-2	I-II	-	-	-
Week 3	I	-	2 (7.10%)	-
Week 4	I	5 (16.66%)	6 (21.40%)	0.68
Week 5	I	6 (20.00%)	7 (25.00%)	0.71
Week 6	I	6 (20.00%)	9 (32.14%)	0.31
Week 7	I	-	6 (21.40%)	-
Week 8	I	-	4 (14.80%)	-
Week 9	I	-	5 (17.80%)	-
Neutropenia				
Week 1-3	I-II	-	-	-
Week 4	I	3 (10.00%)	2 (7.10%)	0.47
Week 5	I	2 (6.66%)	3 (10.71%)	0.36
	II	1 (3.33%)	2 (7.10%)	
Week 6	I	3 (10.00%)	5 (17.80%)	0.32
	II	5 (16.66%)	6 (21.40%)	
Week 7	I	-	3 (10.71%)	-
	II		1 (3.57%)	
Week 8	I	-	2 (7.10%)	-
	II		2 (7.10%)	
Week 9	I	-	3 (10.71%)	-
	II		4 (14.80%)	
Thrombocytopenia				
Week 1-3	I-II	-	-	-
Week 4	I	2 (6.66%)	4 (14.80%)	0.32
Week 5	I	6 (20.00%)	7 (25.00%)	0.70
	II	5 (16.66%)	5 (17.80%)	
Week 6	I	5 (16.66%)	6 (21.40%)	0.51
	II	3 (10.00%)	4 (14.80%)	
Week 7	I	-	2 (7.10%)	-
	II		1 (3.57%)	
Week 8	I	-	3 (10.71%)	-
Week 9	I	-	3 (10.71%)	-
Kidney function test (urea/creatinine)				
Week 1-4	I-II	-	-	-
Week 5	I	3 (10.00%)	1 (3.57%)	0.06
Week 6	I	1 (3.33%)	1 (3.57%)	0.99
Week 7	I	-	1 (3.57%)	-
Week 8	I	-	3 (10.71%)	-
Week 9	I	-	2 (7.10%)	-
GIT toxicity (Diarrhea/nausea/vomiting)				
Week 1-3	I-II	-	-	-
Week 4	I	2 (6.66%)	3 (10.71%)	0.56
Week 5	I	3 (10.00%)	1 (3.57%)	0.38
	II	-	2 (7.10%)	
Week 6	I	2 (6.66%)	-	-
Week 7	I	-	2 (7.10%)	-
Week 8	I	-	2 (7.10%)	-
	II		2 (7.10%)	
Week 9	I	-	2 (7.10%)	-
	II		3 (10.71%)	

Table 4: Acute treatment toxicities during concurrent chemo–radiotherapy treatment.

Durations	Grade	Arm A, (n=30)	Arm B, (n=28)	P value
Anemia				
Week 1-2	I-II	-	-	0.61

Continued.

Durations	Grade	Arm A, (n=30)	Arm B, (n=28)	P value
Week 3	I	3 (10.00%)	2 (7.10%)	
Week 4	I	3 (10.00%)	4 (14.80%)	
Week 5	I	4 (13.33%)	3 (10.71%)	
Week 6	I	5 (16.66%)	6 (21.42%)	
Week 7	I	4 (13.33%)	7 (25.00%)	
	II	2 (6.66%)	1 (3.57) %)	
Neutropenia				
Week 1-2	I-II	-	-	
Week 3	I	3 (10.00%)	2 (7.10%)	
Week 4	I	1 (3.33) %)	2 (7.10%)	
	II	1 (3.33) %)	1 (3.57) %)	
Week 5	I	3 (10.00%)	3 (10.71%)	0.99
	II	1 (3.33) %)	-	
Week 6	I	4 (13.33%)	5 (17.85%)	
	II	1 (3.33) %)	-	
Week 7	I	6 (20.00%)	7 (25.00%)	
	II	2 (6.6%)	3 (10.71%)	
Thrombocytopenia				
Week 1-3	I-II	-	-	
Week 4	I	2 (6.6%)	4 (14.8%)	
	II	-	1 (3.57) %)	
Week 5	I	4 (13.33%)	4 (14.8%)	
	II	1 (3.33) %)	2 (7.1%)	0.97
Week 6	I	2 (6.6%)	3 (10.71%)	
	II	2 (6.6%)	2 (7.1%)	
Week 7	I	3 (10%)	4 (14.8%)	
	II	2 (6.6%)	2 (7.1%)	
	II	-	4 (14.8%)	
Dermatitis				
Week 1-2	I-II	-	-	
Week 3	I	7 (23.33%)	9 (32.14%)	
Week 4	I	15 (50.00%)	16 (57.14%)	
Week 5	I	16 (53.33%)	18 (64.20%)	
	II	5 (16.66%)	5 (17.85%)	
Week 6	I	18 (60.00%)	19 (67.80%)	0.71
	II	5 (16.66%)	6 (21.42%)	
Week 7	I	20 (66.67%)	20 (71.43%)	
	II	1 (3.33) %)	6 (21.42%)	
	III	2 (6.66%)	3 (10.71%)	
Oral mucositis				
Week 1-2	I-II	-	-	
Week 3	I	8 (26.67%)	10 (35.70%)	
Week 4	I	1 (3.33%)	1 (3.57%)	
	II	12 (40.00%)	12 (42.80%)	
Week 5	I	15 (50.00%)	12 (42.80%)	
	II	5 (16.66%)	6 (21.42%)	0.97
Week 6	I	18 (60.00%)	15 (53.57%)	
	II	8 (26.67%)	10 (35.70%)	
	III	-	3 (10.71%)	
Week 7	I	15 (50.00%)	16 (57.14%)	
	II	10 (33.33%)	10 (35.70%)	
	III	3 (10.00%)	5 (17.85%)	
Odynophagia				
Week 1-2	I-II	-	-	0.71
Week 3	I	6 (20.00%)	7 (25.00%)	
Week 4	I	10 (33.33%)	10 (35.70%)	
	II	-	2 (7.10%)	

Continued.

Durations	Grade	Arm A, (n=30)	Arm B, (n=28)	P value
Week 5	I	15 (50.00%)	12 (42.80%)	
	II	5 (16.66%)	6 (21.42%)	
Week 6	I	13 (43.33%)	12 (42.80%)	
	II	6 (20.00%)	10 (35.70%)	
	III	1 (3.33) %)	-	
Week 7	I	8 (26.67%)	9 (32.14%)	
	II	10 (33.33%)	15 (53.57%)	
		2 (6.66%)	6 (21.42%)	

Table 5: Late radiation treatment toxicity in both the arms according to RTOG grade during follow up.

Durations	Grade	Arm A	Arm B	P value
Dermatitis				
Month 3	I	12 (40.00%)	16 (57.14%)	0.28
	II	7 (23.33%)	6 (21.42%)	
Month 6	I	10 (33.33%)	12 (42.85%)	0.56
	II	5 (16.66%)	5 (17.85%)	
Month 9	I	-	2 (7.14%)	-
Oral mucositis				
Month 3	I	16 (53.33%)	10 (35.70%)	0.09
	II	3 (10.00%)	5 (17.85%)	
	III	2 (6.66%)	3 (10.71%)	
Month 6	I	7 (23.33%)	8 (28.57%)	0.28
	II	2 (6.66%)	1 (3.57%)	
Month 9	I	2 (6.66%)	3 (10.71%)	0.57
Xerostomia				
Month 3	I	15 (50%)	12 (42.85%)	0.38
	II	5 (16.66%)	5 (17.85%)	
Month 6	I	10 (33.33%)	12 (42.85%)	0.46
	II	5 (16.66%)	6 (21.42%)	
Month 9	I	5 (16.66%)	5 (17.85%)	0.48
	II	1 (3.33%)	2 (7.14%)	
Subcutaneous fibrosis				
Month 3	I	6 (20.00%)	8 (28.57%)	0.46
	II	-	1 (3.57%)	
Month 6	I	5 (16.66%)	8 (28.57%)	0.29
	II	-	2 (7.14%)	
Month 9	I	8 (26.66%)	8 (28.57%)	0.67
	II	3 (10.00%)	5 (17.85%)	
	III	3 (10.00%)	3 (10.71%)	

DISCUSSION

Treatment of advanced head and neck squamous cell carcinoma (HNSCC) has been an intensive debate in the past. Achieving local control (LC) for long- term still remains a challenge. Combined modality treatment radiotherapy along with chemotherapy has been the standard treatment for non-resectable advance diseases. Thus, different trials and strategies are needed to offer long term local control with less toxicity and more efficacy. In order to improve the LC helping to predict tumour response, overall treatment outcome and survival, controlling micro-metastasis, organ preservation or improving surgical outcomes, and tumour shrinkage several courses of ICT have been added to improve the survival benefits for HNSCC. Most patients presented with advanced stage due to unawareness of the diseases or due to financial issues or family burden.

Patients' characteristics

In both the arms male to female ratio were 3.39:1, this finding is similar to the study conducted by Minu et al showing male to female ratio 3:1.[16] The median age of the study population was 60 years and more than 59% of the patients were above 50 years, which was similar to a study conducted by Sanghera et al in which the median age was 58 years.[17] Smoking, alcohol and tobacco chewing were most common risk factors among most of the patients in both the arms which was similar to the study done by Hashibe et al for tobacco and alcohol was 72% for head and neck cancer, of which 4% was due to alcohol alone,

33% was due to tobacco.[18] Patients with KPS>70% were recruited among both arms with KPS of 80% were the maximum number of patients which was similar to the study conducted by Gupta et al in which most patients had a KPS of 80%.[19]

Tumour characteristics

Oral cavity and laryngeal cancers are the most common HNCs similar to study conducted by Mathur et al showing oral cavity cancer as the commonest followed by cancers arising from larynx, hypopharynx, oropharynx, salivary gland and nasopharynx.[20] Majority of patients in this study presented with stages IVA followed by stage IVB and stage III which was similar to the study conducted by Laursen et al showing majority of the patients in their study presenting with stage IVA.[21] The most common tumour and nodal stage of the patients who presented in this study were tumor stage T3 (50.82%) and nodal stage N2 (59.02%) which was similar to the study conducted by Gupta et al which demonstrated T3 (58%) and N2/N3 (52.6%) as the most common N stage. Most common histology grade was moderately differentiated followed by poorly differentiated and undifferentiated followed by well differentiated with 31.14%, 24.59%, 24.59%, 18.03% respectively which was similarly to the study conducted by Proceddu et al which showed that moderately differentiated was the most common histology grade with 41% in their study.[22]

Toxicities

Acute ICT toxicities were slightly higher in arm B as compared to arm A, which also contributed to an increase in overall treatment time in arm B but no statistical differences were observed between both the arms.

The incidence and severity of oral mucositis in ICT were assessed and compared between the arms. In both the arms the incidence of oral mucositis was first observed at 5th week with grade I and II slightly more in arm B and exhibited a higher incidence of oral mucositis in the later weeks as compared to arm A, which indicate more severe mucositis were seen in the three-cycle regimen. This finding suggests that the additional cycle of chemotherapy may increase mucosal toxicities which was similar to a study conducted by Paccagnella et al which reported an increased incidence of oral mucositis severity with higher cumulative chemotherapy doses.[23]

Anemia incidence and severity in both the arms increased over time, it was first observed by 3rd week with Arm B showing a slightly higher than arm A. The increased chemotherapy dose in arm B likely contributed to the higher anemia rates. Neutropenia incidence was similar in both arms, it was first observed at 4th week with 3 patients (10%) in arm A and 2 patients (7.1%) in arm B, with slight increases in severity in arm B by 6th week. Thrombocytopenia was also observed in both arms by 4th week, during ICT treatment which shows slightly more in arm B as compared to arm A with more patients having thrombocytopenia in the subsequent week. These findings were similar with study conducted by Bhide et al and study conducted by Hitt shows higher toxicity with 3 cycle chemotherapy group.[24,25]

Kidney function test was also assessed every week during the ICT which show similar toxicity incidence between both the arms starting at 5th week with grade 1 toxicity and similar pattern in both the arms. Gastrointestinal toxicities like nausea and vomiting were first observed at 4th week in both the arms. In arm A grade 1 toxicity showing at 4th week, 5th and 6th weeks were 6.66%, 10%, 6.66% respectively whereas in arm B grade I toxicity shows similar pattern to arm A with grade II toxicity seen at 5th, 8th and 9th weeks in arm B. Since in the present study we mainly observed grade I and II toxicity, it was against the study conducted by Somani et at which shows the main toxicity was grade III and IV.[26]

Acute treatment toxicities during the concurrent chemo-radiotherapy treatment was also analyzed and monitored every week during the treatment period in which anemia, neutopenia was first observed from 3rd week in both Arms with slightly higher number of patients seen in arm B but not statistically significant, whereas thrombocytopenia was observed from 4th week of concurrent chemo-radiotherapy. Acute radiation dermatitis toxicities, oral mucositis and odynophagia also develop from 3rd week of treatment. In the present study, grade I, II, III acute toxicities especially radiation dermatitis, oral mucositis and odynophagia were high and developed after 3rd week of radiation which is almost concordance with study conducted by Bhide et al which shows the toxicities in their study were dermatitis 26%, dysphagia 85%, mucositis 78%, neutropenia 3%, anaemia 1%, nausea and vomiting 4% and nephrotoxicity 1% and no grade IV toxicity was seen during chemo-radiation.

Late toxicities including radiation dermatitis, oral mucositis, xerostomia, and subcutaneous fibrosis, were assessed at 3rd, 6th and 9th months of treatment completion. Longer follow-up is needed to better estimate the late adverse events. Here, we observed that late toxicities were slightly higher in arm B however it was not statistically significant. However early and late toxicities did not differ greatly between both study arms.

Response

Post ICT, all patients were assessed which shows regression of the primary site around 43.33% in arm A and 53.57% in arm B and reduction in size of neck nodes around 66.66% in arm A and 78.57% in arm B which shows more than 50% in the reduction in size of the neck node which is similar to the study conducted by Gnanaguru et al.[27] Response rates was observed at the end of treatment in both the arms. In arm A, CR, PR, SD and PD were 6.66%, 50%, 26.66%, 16.66% respectively whereas, in arm B, CR, PR, SD and PD were 10.71%, 64.2%, 14.2%,

10.71% respectively similar to a study conducted by Joshi et al showing CR, PR were 6%, 60% respectively.[28] Both treatment protocols resulted in a majority of participants achieving a complete or PR, indicating comparable efficacy in managing the disease. The rates of SD and PD were also similar between the two arms, suggesting that the treatment protocols were equally effective in preventing disease progression.

Limitations

It was that we have limited follow-up time, small sample size, and the use of 2-D Cobalt-60 teletherapy machine, which have limited sparing to organ at risk. In view of the single institutional randomized control nature of the study and the other limitation it would be difficult to draw any definitive conclusion regarding the local recurrence and the survival pattern from this study. The use of more sophisticated tools and machines with better target volume delineation may produce better tumour response and local regional control.

CONCLUSION

Treatment of locally advanced HNSCC with two-cycle or three-cycle of ICT followed by concurrent chemoradiotherapy are effective in managing locoregionally advanced HNSCC. The three-cycle regimen shows better PR but it is associated with higher incidences of toxicities, including oral mucositis, anemia, neutropenia, thrombocytopenia, and dermatitis. Finally, the present study shows that for locoregional advanced head and neck tumour the treatment responses were almost same in both arms with slightly better in tumour response in arm B but with slightly higher toxicities as compared to arm A. Therefore, the choice of regimen should consider the balance between efficacy and tolerability, with a focus on individual patient general conditions and preferences. Further studied are needed to compare between the cycles of ICT for better response with less toxicities and to improve the local control, overall treatment outcome and survival.

ACKNOWLEDGEMENTS

Authors would like to thank all the staffs of department of radiation oncology, at the institute and also wish to the study participants for their cooperation and active engagement in the research.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee RIMS, Imphal, Manipur was obtained with [No. A/206/REB-Comm(SP)/RIMS/2015/896/234/2022].

REFERENCES

1. Semple CJ, Sullivan S, Dunwoody L, Kernohan WG. Psychosocial interventions for patients with head and neck cancer. Cancer Nursing. 2004;27(6):434-40.
2. Sung H, Ferlay J, Siegel R L, Mathieu L, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.
3. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers. 2020;6(1):92.
4. Bray F, Ferlay J, Soerjomataram I, Rebecca L. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2018;68(6):394-424.
5. Hashibe M, Brennan P, Chuang S-C, Stefania B, Xavier C, Chu C, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev. 2009;18(2):541-50.
6. Mendenhall WM, Werning JW, Pfister DG. Cancer of the head and neck. In: DeVita VT, Hellman S, Rosenberg SA, 10th ed. Cancer: Principals and practice of Oncology. Philadelphia: Wolters Kluwer. 2015;422-4.
7. Gandhi AK, Roy S, Thakar A, Sharma A, Mohanti BK. Symptom burden and quality of life in advanced head and neck cancer patients: AIIMS study of 100 patients. Indian J Palliat Care. 2014;20(3):189-93.
8. Agarwal JP, Nemade B, Murthy V, Laskar SG, Budrukkar A, Gupta T, et al. Hypofractionated, palliative radiotherapy for advanced head and neck cancer. Radiother Oncol. 2008;89(1):51-6.
9. Mukherji SK, Armao D, Joshi VM. Cervical nodal metastases in squamous cell carcinoma of the head and neck: what to expect. Head Neck. 2001;23(11):995-1005.
10. Wolf TG, Hong WK, Fisher SG, Urba S, Endicott JW, Close L, et al. The department of veterans' affairs laryngeal cancer study group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med. 1991;324(24):1685-90.
11. Hong WK and Biomer R. Current concepts: Chemotherapy in Head and Neck Cancer. N. Engl J Med. 1983;308(2):75-8.
12. Bhide SA, Ahmed M, Barbachano Y, Newbold K, Harrington KJ, Nutting CM. Sequential induction chemotherapy followed by radical chemo-radiation in the treatment of locoregionally advanced head- and-neck cancer. Br J Cancer. 2008;99(1):57-62.
13. Goel A, Singla A, Prabhash K. Neoadjuvant chemotherapy in oral cancer: Current status and future possibilities. Cancer Res Stat Treat. 2020;3:51-9.
14. Radiation Therapy Oncology Group. RTOG acute and late Radiation Morbidity Scoring criteria. Available

at: http://www.rtog.org/ResearchAssociates/AdverseEvent Reporting/Acute and late Radiation Morbidity Scoring Criteria.aspx. Accessed on 10 April 2025.
15. Eisenhauer A, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European J of Cancer. 2009;45(2):228-47.
16. Michaelraj MJ, Kuttiappan K, Ramasamy S, Rodrigues FAE, Govindaraj S. Demographic profile and risk factors of head-and-neck squamous cell carcinoma in west Tamil Nadu: A cross-sectional observational study. Cancer Res Stat Treat. 2023;6(2):215-223.
17. Sanghera P, McConkey C, Ho KF, Glaholm J, Hartley A. Hypofractionated accelerated radiotherapy with concurrent chemotherapy for locally advanced squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2007;67(5):1342-51.
18. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev. 2009;18(2):541-50.
19. Gupta T, Agarwal JP, Ghosh-Laskar S, Parikh PM, D'Cruz AK, Dinshaw KA. Radical radiotherapy with concurrent weekly cisplatin in loco-regionally advanced squamous cell carcinoma of the head and neck: a single-institution experience. Head Neck Oncol. 2009;1:17.
20. Mathur P, Kumar SK, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, et al. Cancer Statistics, 2020: Report from National Cancer Registry Programme, India. JCO Glob Oncol. 2020;6:1063-75.
21. Laursen M, Specht L, Kristensen CA, Gothelf A, Bernsdorf M, Vogelius I, et al. An Extended Hypofractionated Palliative Radiotherapy Regimen for Head and Neck Carcinomas. Front Oncol. 2018;8(1):206.
22. Porceddu SV, Rosser B, Burmeister BH, Jonesc M, Hickeya B, Baumannd K, et al. Hypofractionated radiotherapy for the palliation of advanced head and neck cancer in patients unsuitable for curative treatment-hypo trial. Radiother Oncol. 2007;85(3):456-62.
23. Paccagnella A, Ghi MG, Loreggian L, Buffoli A, Koussis H, Mione CA, et al. Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study. Ann Oncol. 2010;21(7):1515-22.
24. Bhide SA, Ahmed M, Barbachano Y, Newbold K, Harrington KJ, Nutting CM. Sequential induction chemotherapy followed by radical chemo-radiation in the treatment of locoregionally advanced head- and-neck cancer. Br J Cancer. 2008;99(1):57-62.
25. Hitt R, Lo´pez-Pousa A, Martínez-Trufero J, Escrig V, Carles J, Rizo A, et al. Phase III study Comparing Cisplatin Plus Fluorouracil to Paclitaxel, Cisplatin, and Fluorouracil Induction Chemotherapy Followed by Chemoradiotherapy in Locally Advanced Head and Neck Cancer. J Clin Oncol. 2005;23(34):8636-45.
26. Somani N, Goyal S, Pasricha R, Khuteta N, Agarwal P, Garg AK, et al. Sequential therapy (triple drug-based induction chemotherapy followed by concurrent chemoradiotherapy) in locally advanced inoperable head and neck cancer patients - Single institute experience. Indian J Med Paediatr Oncol. 2011;32:86-91.
27. Gnanaguru V, Dhanushkodi M, Radhakrishnan V, Kalaiarasi JP, Rajan AK, Selvarajan G, et al. Induction chemotherapy in locally advanced head-and-neck squamous cell carcinoma: Real-world outcome. Oncol J India. 2020;4:105-9.
28. Joshi P, et al. Neo-adjuvant chemotherapy in advanced hypopharyngeal carcinoma. J Oncol. 2019;10(2):123-35.

Cite this article as: Swer D, Singh LJ, Devi YS, Panmei R, Kilari LTG, Babu BM. A comparative study on tumour response and treatment toxicities of two cycles versus three cycles of induction chemotherapy followed by concurrent chemoradiotherapy in the management of locoregional advanced head and neck cancer. Int J Res Med Sci 2025;13:2855-65.