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Research Article

A RANDOMIZED STUDY ANALYZING CLINICAL AND DOSIMETRIC OUTCOME IN LOCALLY ADVANCED HEAD-AND-NECK CANCER TREATED WITH CONFORMAL CHEMORADIATION WITH OR WITHOUT INDUCTION CHEMOTHERAPY

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ABSTRACT

Objective: Squamous cell carcinoma of the head and neck (HNSCC) represents around 10% of new cases in India annually and with a similar trend worldwide. Treatment strategies for stages III and IV HNSCC differ in view of resectability, organ preservation, and medical conditions. Induction chemotherapy (IC) followed by concomitant chemoradiation (CTRT) is widely practiced but Indian data regarding clinical outcomes in the IGRT scenario is still not promising. In this study, we tried to evaluate the dosimetric parameters, response rate, survival, and toxicities as well.

Methods: We started our study in August 2019 with Institutional Ethical Committee approval with 42 patients in the CTRT arm and 40 patients in IC+CTRT arm. Patients in the CTRT arm received radiation (66–70 Gy) with 3 weekly cisplatin 80 mg/m^2. In the induction arm, 2 cycles of taxane, platinum, 5FU were given followed by concomitant radiotherapy with the same dose and cisplatin.

Results: Overall response rates (CR+PR) were 69% versus 72.5% (p=0.06). 2 years overall survival (OS) were 66.7% versus 69.5% (p=0.91). Median disease-free survival were slightly better in the IC+CTRT arm but mean OS was comparable. Mean values of clinical target volume, planning target volume, Spine Dmax, and parotid were lower in the induction arm (p<0.05). Patients with IC experienced more hematological toxicities (p<0.01).

Conclusion: IC followed by CTRT offers better dosimetric outcome, slightly better progression-free survival, with more hematological toxicities and no OS benefit.

Keywords: Induction chemotherapy, Concurrent chemoradiation, Survival, Response, Locally advanced head-and-neck cancer.

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INTRODUCTION

Carcinoma of the head-and-neck region represents around 10% of new cases in India annually and with a similar trend worldwide [1]. The standard of care of these patients depends on the anatomic site, stage, resectability, performance status, and other medical conditions. Oral cavity cancers are primarily addressed with surgery, while chemoradiation remains a cornerstone in oropharyngeal and hypopharyngeal cancers. Unfortunately, around 50% of the head-and-neck carcinoma cases present at a locally advanced stage. Treatment strategies for stage III and IV squamous cell carcinoma of the head and neck (HNSCC) differ because of resectability, organ preservation, and medical conditions. The recent update on the meta-analysis of chemotherapy in head-and-neck cancer (MACH-NC) clearly showed that concomitant chemoradiation (CTRT) is beneficial in non-metastatic squamous cell head-and-neck cancer [2]. However, there are more things to explore in treating unresectable squamous cell head-and-neck cancer given organ preservation, quality of life, dosimetric constraints in organs at risk, and any undue delay in starting CTRT and radiological response. Induction chemotherapy (IC) is frequently used in clinical practice for its role in organ preservation but its impact on overall survival (OS) has been questioned for years [3-5]. There are well-cited studies in the literature that confirmed that the addition of a taxane to the usual Platinum and 5FU (PF) regimen brings better response and leads to improved OS in locally advanced HNSCC [6-8].

The quality of life in these patients is also a point to ponder about. Apart from radiation-induced skin and hematological toxicities, late toxicity like xerostomia may give rise to a myriad of symptoms as saliva is vital for normal oral function including lubrication, deglutition, and maintaining normal flora of the oral cavity. The impact of IC in dosimetric constraints of OAR like parotid in locally advanced HNSCC has not been evaluated well enough, especially in the Indian context.

In this study, we intended to evaluate the impact of the addition of IC to concurrent chemoradiation given the dosimetric parameters, response rate, survival, and toxicities in locally advanced, unresectable HNSCC.

METHODS

Study design

This was an open-label, prospective, randomized, single institutional interventional study. This study was conducted after Institutional Ethical Committee approval, from Aug 2019 to July 2022. Patients aged 18–70 years, with biopsy-proven HNSCC region (except nasopharynx), clinic-radiologically locally advanced, were included in our study. Patients with prior surgery or chemoradiation in the head and neck, with poor performance status (ECOG PS >2), and with uncontrolled comorbid conditions were excluded from this study.

The sample size of this prospective clinical study was analyzed based on a radiological response rate of 21.2% (control) versus 50% (study) from a landmark study [9]. We assumed the alpha (probability of type I error) to be 0.05 and the power of the study to be 80%, then the sample size (n) becomes 42 in each arm (total 84).

Method of randomization
We randomized the participants into two arms using a random number table. All patients had submitted written informed consent and the study was conducted following the Declaration of Helsinki.

Treatment plan
Patients in arm A received concurrent chemoradiation, while in arm B, they received IC followed by concurrent chemoradiation. Conventional fractionation was used in both arms, delivering a dose of 60–66 Gy. IC and concurrent chemotherapy were as per standard protocol [4,7].

Response evaluation
We analyzed the clinical outcome as well as toxicities by doing a CECT/magnetic resonance imaging 6–8 weeks after treatment completion and then at 6 and 12 months [10,11]. Progression-free survival (PFS) was evaluated from the date of randomization up to the date of first progression, second primary malignancy, or death from any cause. Patients not progressing and alive at the time of the analysis were censored at the last assessment date.

Statistical analysis
A total of ninety-four patients were initially accrued for the study, and patients who defaulted or could not adhere to the protocol were excluded at the time of final analysis. Analyses of PFS were carried out on the intent-to-treat population. Survival analysis was evaluated by the Kaplan–Meier method and log-rank test. The response rate was assessed by the Chi-square test, while the unpaired t-test compared the dosimetric means.

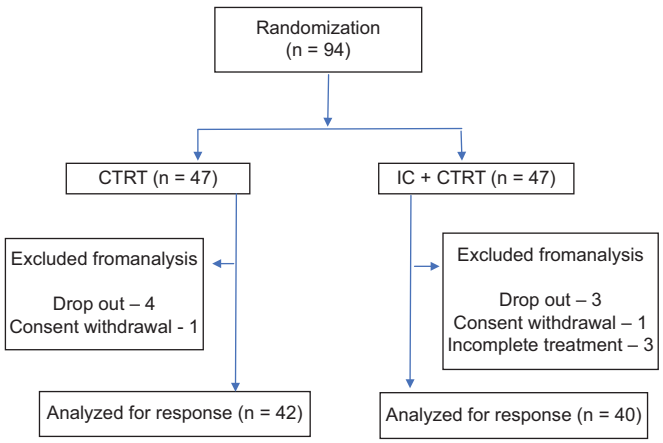

Fig. 1: Patient flow

RESULTS

The median age of the study population was 54 years, with a slight male predominance (M: F – 1.6:1) (Fig. 1). Median follow-up time was 32 months (range 19–40 months). The baseline characteristics of the patients in both arms were equivocal (Table 1). Case distribution as per the primary anatomy site was also comparable among the groups. Stage III cases were slightly more in the CTRT arm (73.8%), while there was a preponderance of stage IV cases in the induction arm, 45% versus 26% (p=0.06). Stage stratification by T (Tumor size) and N (nodal) staging was also non-significant. We observed that technical unrespectability was the primary reason for chemoradiation, while around 20% of cases were accrued for organ preservation, mainly for larynx preservation.

We observed that the overall response rate (ORR=CR+PR) was slightly better in the induction arm (69% vs. 72.5%) but was not statistically significant. Thirteen patients (30.9%) and 11 patients (27.5%) progressed radiologically and clinically in the CTRT and induction arm, respectively (Table 2). The mean duration of ORR was 34.2 months (95% confidence interval [CI] 32.24–35.94) in the CTRT arm, while it was 36.12 months (95% CI 34.74–37.70) in the induction arm (p=0.30).

Survival analysis showed that neither PFS nor OS was statistically significant between the arms. Two-year OS rate was 66.7% in the chemoradiation arm, while it was 69.5% in the induction arm (p=0.91) (Figs. 2–4). Mean PFS and OS were also equivocal between the arms. The median value for both PFS and OS was not achieved. On subsite analysis, it was noted that oropharyngeal cancer had better local control with IC (78.5% vs. 83.3%) and it was evident in the PFS also (Fig. 3).

Radiation-induced oral mucositis was the chief adverse event noted during the study (Table 3). In the CTRT arm, nineteen patients experienced grade 3/4 oral mucositis, and eighteen patients experienced the same in the induction arm. Although overall hematological toxicity was not alarming, we noted that the patients in the induction arm significantly experienced more grade III/IV hematological toxicity (7% vs. 27%). Neutropenia followed by anemia was the most common noted hematological toxicity and these were managed conservatively. Both gastrointestinal and skin toxicity were comparable between the arms. There were no significant unscheduled treatment breaks in either arm. Two patients in the CTRT arm had a treatment break for more than 3 days, while we had to stop radiation therapy in four patients

Table 1: Baseline characteristics of the patients

Patient characteristics	Concomitant chemoradiation (n=42)	Induction chemotherapy+concomitant chemoradiation (n=40)	p-value
Median age (range)	51 (29–65)	54 (31–66)	0.65
Primary site			
Oral cavity	18	20	0.80
Oropharynx	14	12	
Hypopharynx/larynx	10	08	
Stage III	31	22	0.06
Stage IV	11	18	
T Stage			
T3	30	26	0.34
T4	12	14	
Nodal stage			
N1	18	11	0.31
N2	18	21	
N3	06	08	
Reason for chemoradiation			
Unresectable	31	30	0.98
Medically inoperable	02	02	
Organ preservation	09	08	

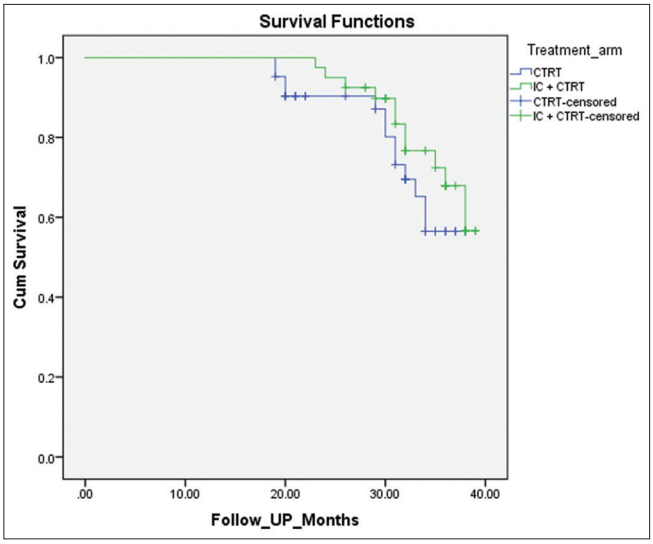

Fig. 2: Kaplan–Meier survival curve for progression-free survival

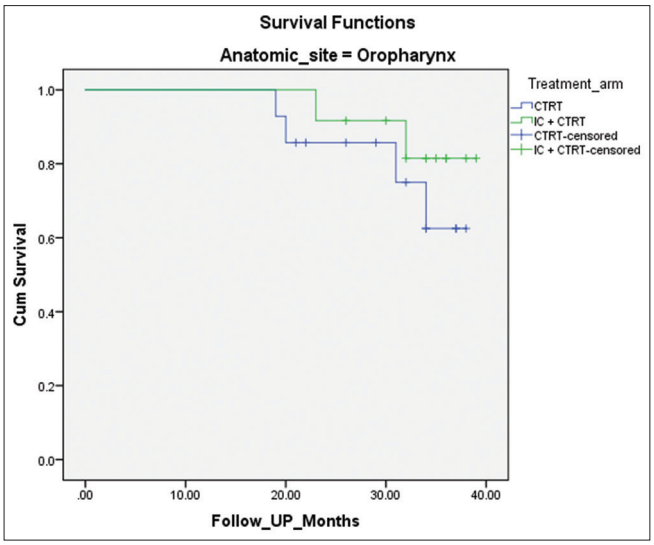

Fig. 3: Progression-free survival comparison of the oropharyngeal cases

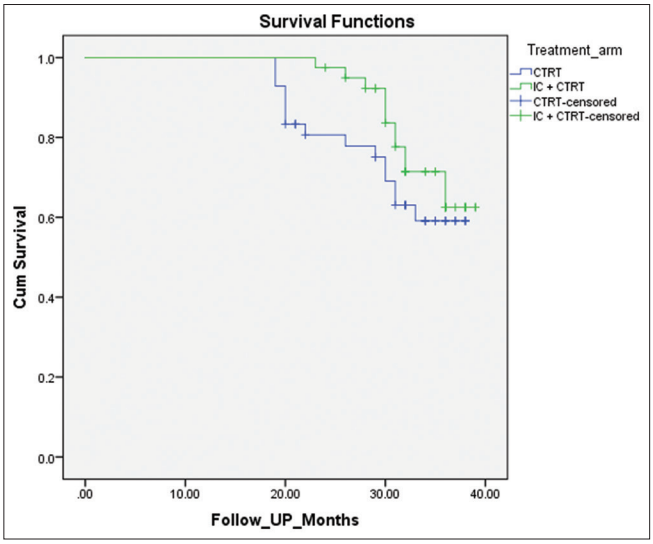

Fig. 4: Overall survival between two arms

in the induction arm, for more than 3 days. Gap calculations and dose correction were allowed wherever applicable in both arms. The median dose of radiation was 66 Gy in both arms (range 66–70 Gy).

In view of the analysis of dosimetric data, we found that the clinical target volume (CTV) and planning target volume were significantly smaller in the induction arm ($p<0.01$). The mean dose to the spinal cord and contralateral parotid was also significantly lesser in the induction arm (Table 4). All other dosimetric parameters were comparable. All the radiation plans were executed by a fixed team of physicists and checked by a senior radiation oncologist having more than 10 years of clinical practice.

DISCUSSION

The treatment paradigm for locally advanced HNSCC has evolved over the past several decades, but the multidisciplinary approach for the management of LA-HNSCC is argued among oncologists. The most recent update from the landmark MACH NC meta-analysis showed that CTRT is the mainstay treatment for LA HNSCC. However, study also pointed out that distant failure rates were significantly lower in the induction arm, and the greater number of treatment-related deaths in the induction arm could be attributed to poor patient selection, poor performance status, and lack of prophylactic G-CSF [12,13]. We should also keep in mind that few induction (Taxane PF [TPF]) trials were not included in the MACH NC Meta-analysis, there were confounding factors such as chemoradiation or radiotherapy as a comparator and few trials included the addition of cetuximab [14,15]. The role of IC in LA HNSCC is being explored with the basic premise of reducing the extent of surgical resection, improving local control, and decreasing distant metastasis, thereby improving treatment outcomes by reducing mortality and morbidity.

The present study did not reveal any statistically significant difference in terms of local control or survival between the two groups. However, there was a trend for better overall response (ORR) in the induction arm along with some definitive dosimetric advantages. To the best of our knowledge, this is the first study incorporating dosimetric data in the context of chemoradiation in LA HNSCC with or without IC (TPF). The 2-year local control rate and OS rate of our study were also comparable to the existing literature. In this study, we have modified the conventional induction treatment plan using a 1-day slow infusion of 5FU as per institutional logistics. There have been attempts to use a modified TPF regimen to decrease its toxicity without altering the efficacy, but the available data are scarce and mixed [16,17]. Accelerated repopulation is also a noted radiobiological concern in head-and-neck squamous cell cancer, to address this issue, we started CTRT 2 weeks after completion of induction TPF, while several trials used a 3–5-week gap. This could have led to a non-significant better outcome in the induction arm, along with a tolerable greater hematological toxicity.

A recent Indian study has shown the benefit of IC in unresectable oral cavity cancer. That study showed around 23.8% of patients achieved resectability and they had a significantly better median OS [18]. Our study showed that the overall response rate was greater in the oral cavity subsite with (65% vs. 50%) IC, though these patients did not undergo surgical resection and this trend looked promising.

Many studies showed better radiological response with IC [9,19,20]. Another recent study from Brazil showed that IC improved numerous aspects of swallowing and had a positive impact on quality of life [21]. Our study had shown better parotid sparing, spinal cord sparing, and low volume CTV in the induction arm though there was no discrepancy between the two groups given the anatomic subsite and TNM staging. We consider this as the biggest takeaway from this study and wish to correlate it with quality-of-life data in subsequent analysis.

Contrary to our study, the combined study of two national cohorts in Taiwan opined against the use of IC [22]. We also noted that the radiological complete response was more in favor of the induction arm (37.5% vs. 20%), and the 2-year larynx preservation rate was

Table 2: Response rate and survival of the patients

Parameters	Concomitant chemoradiation arm			Induction chemotherapy+ Concomitant chemoradiation Arm			p-value
	CR	PR	PD	CR	PR	PD	
Radiological response							
Oral cavity	03	06	09	04	09	07	0.09
Oropharynx	06	05	03	05	05	02	
Hypopharynx/larynx	02	07	01	03	03	02	
Mean PFS (months)	34.20			36.18			0.30
Mean OS (months)	32.11			34.24			0.64
2 year PFS (%)	69			72.5			0.06
2 year OS (%)	66.7			69.5			0.91

OS: Overall survival, PFS: Progression-free survival

Table 3: Radiation-induced toxicities among patients

Toxicities	Concomitant chemoradiation	Induction chemotherapy+ concomitant chemoradiation	p-value
Oral mucositis			
Grade I/II	23	22	0.69
Grade III/IV	19	18	
GI toxicity			
Grade I/II	40	38	0.67
Grade III/IV	2	2	
Hematological toxicity			
Grade I/II	39	29	<0.01
Grade III/IV	03	11	
Skin toxicity			
Grade I/II	31	28	0.18
Grade III/IV	11	12	

Table 4: Dosimetric data of the patients

Dosimetric parameters	Concomitant chemoradiation	Induction chemotherapy+ concomitant chemoradiation	p-value
Clinical target volume (cc)	424.76	344.41	<0.01
PTV (cc)	680.93	576.11	<0.01
PTV_D95 (%)	96.72	96.06	0.07
PTV_D90 (%)	98.61	98.11	0.09
PTV_V95 (%)	96.42	95.83	0.38
PTV_V90 (%)	99.52	98.66	0.31
SPINE Dmax (Gy)	44.20	40.74	0.02
Contralateral parotid mean dose (Gy)	24.97	22.10	0.01
Brainstem Dmax (Gy)	38.46	34.66	0.28
Optic Nerve Dmax (Gy)	8.27	5.97	0.89
Pharyngeal constrictor mean dose (Gy)	49.84	49.76	0.52
Median Radiation dose (Gy) (range)	66 (66–70)	66 (66–70)	0.72

PTV: Planning target volume

comparable with current evidence. Although the long-term results of the RTOG 91-11 trial showed the superiority of CTRT in preserving functional larynx, we should also consider the fact that the radiation techniques have evolved over the past 20 years. Moreover, there are discrepancies regarding the definition of the functional larynx from "organ at place" to "intake of only sieved food preparations." A recent phase II study on hypopharyngeal cancer showed that the addition of IC failed to demonstrate any survival benefit over CTRT [23-25].

Our study had some limitations. We noted slightly better outcomes with IC in oropharyngeal cancer, but due to a lack of information regarding HPV status, the observation could not be generalized as a whole. This study lacks xerostomia-based QOL assessment to validate the dosimetric advantage with IC in parotid gland sparing. A multi-institutional randomized study with more sub-site specific objectives with greater median follow-up time is required.

CONCLUSION

Although a clear advantage of IC over CTRT could not be established in the present study, it certainly raised a few positive aspects. In our opinion in cases of bulky tumors close to a critical organ at risk or to bridge the gap between diagnosis and definitive CTRT, IC can be used with proper case selection. The clinical correlation also needs to be established with longer follow-up, demanding further research.

CONFLICT OF INTERESTS

None.

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Nil.

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