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COMPARISON BETWEEN INDUCTION CHEMOTHERAPY FALLOWED BY CONCURRENT CHEMOTHERAPY VERSUS CONCURRENT CHEMOTHERAPY ALONE IN HYPOPHARNGEAL CARCINOMA-A PILOT STUDY

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ABSTRACT

Background: The incidence of distant metastasis is quite high in patients of Hypopharyngeal cancers compared to concurrent chemoradition alone. **Aims and objectives:** To assess and compare 1) The loco-regional response and patterns of failure in carcinoma hypopharynx patients treated with induction chemotherapy followed by chemoradiation versus chemoradiation alone. 2) The toxicity profile in patients treated in 2 arms. **Materials and Methods:** 40 patients,(20 prospective for Arm A, 20 retrospective for Arm B presenting with T1N+, T2/T3 any N, M0 stages of Carcinoma Hypopharynx were enrolled. In Arm A, patients received Induction Chemotherapy (2 cycles of 3 weekly Inj.Paclitaxel 175 mg/m^2 & Inj.Cisplatin 70mg/m^2) followed by concurrent chemoradiation (2cycles of 3 weekly Inj.Cisplatin 70mg/m^2. In Arm B, patients received Concurrent Chemoradiation alone (2cycles of 3 weekly Inj.Cisplatin 70mg/m^2 .The radiation done was same in both arms at 7000cGy in 35 fractions at 2Gy/fraction. **Results:** In Arm A, showed more responses compared to Arm B. At 6 months, the complete response rate for Arm A was 88.9% compared to 66.7% in Arm B, though the difference was not statistically significant. None of the patients in Arm A developed progressive disease as opposed to 2 (10%) patients in Arm B. Toxicity profile of mucositis, haematological and dysphagia in both Arms were comparable. **Interpretation & Conclusion:** Sequential therapy (ICT+CTRT) was well tolerated and showed favorable improvement in tumour response rates and reduced treatment failure compared to patients treated with CTRT alone. Thereby sequential therapy offers a safe and effective means of management in T1N+, T2/T3 any N, M0 stages of Carcinoma Hypopharynx patients.

KEYWORDS: Hypopharynx cancer; Radiotherapy; Sequential therapy; Induction Chemotherapy; Chemoradiation.

INTRODUCTION

Cancers of hypopharynx comprise less than 1% of all cancers in the world. In India, it is the fifth most common cancer among men and tenth common cancer among women. The incidence rate of hypopharyngeal cancers in India is more than four times as high in men as in women.[1] With increased usage of tobacco by men and women, incidence of hypopharyngeal carcinomas is increasing. The consolidated data representing cancer prevalence as per International Agency for Research on Cancer, World Health Organization (WHO) and ICMR report is shown in table 1.

Table 1: Prevalence of Oro-Hypopharyngeal Cancer in India in comparison to world.

Description	World	India	India As % of World
Total Cancer	15,362,289	664,538	4.3%
Head & Neck	880,174	137,944	15.6%
Oro-Hypopharynx	142,387	38,691	27.2%

The incidence of distant metastasis is the highest in patients of hypopharyngeal cancers compared to cancers of oral cavity, oropharynx, nasopharynx and larynx. In the patients who have been treated, even the locoregional failure was highest at 43.7% in hypopharyngeal carcinomas when compared to the other cancers.[2] Until the early 1990s, the standard treatment for locally advanced larynx and hypopharynx squamous cell carcinoma was total laryngectomy followed by conventional radiotherapy. Different treatments have since been tested, including partial surgery, radiotherapy, and chemotherapy, without optimal schedule. The main

courses of failure are locoregional recurrences and distant metastases.[3] Total laryngectomy is one of the surgical procedures that is most feared by patients. This procedure has a negative impact on patients, with tracheotomy, loss of natural voice, social isolation, loss of employment, and depression. To preserve larynx function, chemotherapy before surgery, or induction chemotherapy, had been developed. Induction chemotherapy with cisplatin (P) and 5-fluorouracil (F) followed by radiotherapy in patients who respond to chemotherapy was considered as an alternative to total laryngectomy.[4]

Addition of taxanes to the induction chemotherapy regimen showed improved overall survival, progression free survival and laryngectomy free survival. The addition of taxanes did not show any significant increase in toxicities when compared to the previous PF regimen.[5] The main side effect of induction chemotherapy is neutropenia while the radiotherapy for hypopharyngeal cancers typically involves irradiation of a large area of normal mucosa and leads to mucositis and dysphagia. The present study has been undertaken with the intention of treating these patients in the most appropriate manner using induction chemotherapy followed by concurrent chemoradiation and comparing the results with patients treated by concurrent chemoradiation.

Induction Chemotherapy and concurrent chemo radiation (Sequential Therapy)

Recently, there has been renewed interest in the concept of induction chemotherapy approaches for patients with loco regionally advanced H&N cancer. In an effort to examine the potential for organ preservation in patients with advanced cancers of the hypopharynx, the EORTC conducted a randomized trial for patients with tumors that would require total laryngectomy as the surgical approach. This trial randomly allocated patients to induction chemotherapy with cisplatin and 5-fluorouracil (5-FU) followed by definitive radiation versus primary surgical resection and postoperative radiation. With a median follow-up of 10 years, this trial demonstrated no significant difference in 5- or 10-year overall survival or progression-free survival. Of note, two-thirds of living patients in the chemoradiotherapy arm were able to retain their larynxes.[5]

More recently the introduction of taxane-containing regimens has been demonstrated to improve outcomes in patients receiving induction chemotherapy. Three randomized trials have been reported that compare induction 5-FU and cisplatin versus 5-FU, cisplatin, plus a taxane. ICT + CTRT is the preferred treatment at present for T1N+, T2/T3 any N, M0 stages of Carcinoma Hypopharynx. The aggressive approaches certainly appear worthy of consideration for H&N subsites such as hypopharynx where the organ preservation is desirable and overall outcomes are poor, with both locoregional control and distant metastases presenting a formidable challenge. Patients with good performance status, no contraindications to taxanes or platins, a high tumor burden or advanced nodal disease may be optimal candidates for this approach.[7]

Lee-Ping Hsu et al. demonstrated in a study of 735 patients with HNSCCs who were treated between 1991 and 2000, all of whom had at least 2 years of follow up, that the incidence of distant metastasis is the highest in patients of Hypopharyngeal cancers compared to cancers of oral cavity, oropharynx, nasopharynx and larynx. In the patients who have been treated, it was demonstrated that the locoregional failure was highest at 43.7% in hypopharyngeal carcinomas when compared to the other cancers.[8]

Pacagnella et al demonstrated in a study of 101 patients with Stage III and IV locally advanced Squamous cell Carcinomas of Oral cavity, Oropharynx and Hypopharynx, were randomly assigned to receive CT/RT alone or three cycles of followed by the same CT/RT. Induction TPF followed by CT/RT was associated with higher radiologic Complete Response (CR) of 50% and Partial response (PR) of 28.2% against CR 21.3% and PR 61.7% in patients treated with CT/RT alone. They concluded that Induction Chemotherapy followed by CT/RT was associated with higher radiologic CR in patients with locally advanced SCCHN with no negative impact on CT/RT feasibility and similar toxicities.[9]

R. Haddad et al. in a randomized study enrolled 145 patients with locally advanced squamous cell carcinomas of Oropharynx, Oral cavity, Larynx, Hypopharynx with stages T3, T4, any N2/N3 except T1N2 and compared Induction chemotherapy with 3 cycles of 3 weekly TPF followed by concurrent chemoradiotherapy of weekly docetaxel or carboplatin and 70Gy in 35 fractions versus concurrent chemoradiotherapy with Cisplatin on days 1 and 22 of radiation and 70Gy in 35 fractions alone. After median follow up of 49 months, 3-year overall survival was 73% in the induction chemotherapy followed by chemoradiotherapy group and 78% in the chemoradiotherapy alone group. Their study also found distant metastasis of 7% in ICT followed by CT/RT as against 11% in patients treated with CT/RT alone with both arms showing comparable toxicities and comparable local control. They concluded that addition of induction chemotherapy remains appropriate approach for advanced disease with high risk for local or distant failure.[10]

Blanchard et al. in a study compared Cisplatin plus fluorouracil (PF) induction chemotherapy with Taxane (docetaxel or paclitaxel), cisplatin, and fluorouracil (Tax-PF) in randomized trials in loco regionally advanced head and neck cancers (LAHNCs). Data from five randomized trials representing 1,772 patients were identified. The median follow-up was 4.9 years. Their analysis showed that Tax-PF significantly improves OS, PFS, head and neck cancer mortality, and locoregional

and distant failure compared with PF for locally advanced HNSCC. They also stated that Tax-PF is also associated with a better compliance with induction chemotherapy and more patients in the Tax-PF group proceeded to concomitant chemoradiotherapy, likely reflecting the higher response rate. They concluded that the meta-analysis showed the superiority of Tax-PF over PF as induction chemotherapy and its precise role in the management of LAHNC remains to be determined.[11]

Hitt et al. in a phase III study compared the antitumor activity and toxicity of the two induction chemotherapy treatments of paclitaxel, cisplatin, and fluorouracil (PCF) versus standard cisplatin and FU (CF), both followed by chemoradiotherapy (CRT), in locally advanced head and neck cancer (HNC). They included 382 biopsy-proven, previously untreated; stage III or IV locally advanced SCCHN. Patients with complete response (CR) or partial response of greater than 80% in primary tumour received additional CRT (cisplatin 100 mg/m2 on days 1, 22, and 43 plus 70 Gy). They found that the CR rate was 14% in the CF arm v 33% in the PCF arm (p <.001) and median time to treatment failure was 12 months in the CF arm compared with 20 months in the PCF arm (p<.006) .The overall survival was longer in patients treated with PCF (OS; 37 months in CF arm v 43 months in PCF arm).[12]

Posner et al. analysed outcomes in a subgroup of assessable Laryngeal and Hypopharyngeal cancers (LHC) patients enrolled in TAX 324, a phase III trial of sequential therapy comparing docetaxel plus cisplatin and fluorouracil (TPF) against cisplatin and fluorouracil (PF), followed by chemoradiotherapy. Among 501 patients enrolled in TAX 324, 166 had LHC (TPF, n = 90; PF, n = 76) and the patient characteristics were similar between subgroups. Median OS for TPF was 59 months versus 24 months. Median PFS for TPF was 21 months versus 11 months for PF. The study concluded that in locally advanced LHC, sequential therapy with induction TPF significantly improved survival and PFS versus PF.

Lefebvre et al. in a study reported the 10-year results of the EORTC trial 24891 comparing a larynx-preservation approach to immediate surgery in hypopharynx squamous cell carcinoma. Two hundred and two patients were randomized to either the surgical approach (total laryngectomy with partial pharyngectomy and neck dissection, followed by irradiation) or to the chemotherapy arm up to three cycles of induction chemotherapy (cisplatin 100 mg/m2 day 1+5-FU 1000 mg/m2 day 1–5) followed for complete responders by irradiation and otherwise by surgery followed by adjuvant RT. The 10-year OS rate was 13.8% in the surgery arm and 13.1% in the chemotherapy arm. The 10-year PFS rates were 8.5% and 10.8%, respectively. In the chemotherapy arm, the 10-year SFL rate was 8.7%. Local or regional failure rates did show a significant reduction in distant metastases as a site of first failure (p=.041). They came to the conclusion that Induction chemotherapy strategy did not compromise disease control or survival and allowed more than half of the survivors to retain their larynx.[13]

MATERIALS AND METHODS

The source of data for the study are patients presenting to the department of Radiation oncology, with T1N+, T2/T3 any N stages of Carcinoma Hypopharynx. The duration of the study is one and half year.

ARM A (prospective study) - Sequential therapy (Induction Chemotherapy followed by concurrent Chemoradiation)

ARM B (retrospective study) - Concurrent Chemoradiation alone.

The total sample size chosen is 40 patients (20 in each arm). Age 20 to 65 years, both sexes, Performance Status-0-3 (ECOG Criteria), locally advanced T1N+, T2/T3 any N cases of carcinoma hypopharynx; Patients with histologically proven squamous cell carcinoma of hypopharynx were included in the study. The patients with Metastatic disease, Performance status more than 3 (ECOG criteria), Previous irradiation to head and neck area, Patients who have undertaken primary surgery were excluded from the study.

The pretreatment evaluation was done based on the following factors: Complete history and physical examination, Detailed clinical examination for primary and neck nodes, Biopsy or FNAC from primary and/or neck nodes, Indirect Laryngoscopy/ Fibreoptic scopy, Dental prophylaxis and repairs if necessary, Laboratory tests – Complete blood and Platelet counts, Liver Function Test, Renal Function Test, Radiological investigations – Chest X – Ray, Contrast CT Head and neck.

Informed written consent of the patient

When all the investigations were within the normal limits, patient's written consent was taken after explaining the nature of the disease, its treatment options and side effects in their own vernacular language. Patient was counseled about the ill effects of tobacco and alcohol consumption and asked to discontinue the same. They were also explained regarding oral hygiene, nutrition and precautions to be taken throughout the treatment. The patients were also explained about the current clinical trial.

TREATMENT PLAN SCHEME

Chemotherapy

Induction Chemotherapy

The drugs PACLITAXEL and CISPLATIN were used as double agent induction chemotherapy before concurrent chemo radiation after discussion and approval of the Dept. of Medical Oncology of our institute. The dosage of Paclitaxel was 175mg/m^2 3 weekly for 2 cycles weekly for 2 cycles. The patient was started on

chemotherapy after adequate hydration and pre medication.

Concurrent Chemotherapy
The drug CISPLATIN was used as a single agent concurrently with the radiotherapy. The dosage used was 70 mg / m^2 3 weekly for 2 cycles. The first cycle was administered on the first day of radiation. The patient was started on chemotherapy after adequate hydration and pre medication.

Target Volume and Technique
The treatment plan included bilateral parallel opposed fields covering PTV to a dose of 40 Gy in 2 Gy per fraction and a bilateral parallel opposed off-cord field with posterior electron field to a dose of 20 Gy in 2 Gy per fraction and a lower anterior neck field to a dose of 50 Gy in 2 Gy per fractions covering the lower neck. The CTVT was then boosted to a dose of 10 Gy in 2 Gy per fractions. All patients were treated based on CT scan simulation and planning. The portal verification was done using Electronic Portal Imaging Device (EPID) generated image and compared with Digitally Reconstructed Radiographs (DRR).All patients were treated by Clinac Linear accelerator machine with source to axis distance (SAD) of 100 cm using 6MV energy.

Patient Evaluation
During treatment, the patient was explained about the care of irradiated site, precautions, and diet modifications. The weight of the patient and acute reactions were documented on weekly basis. The grading of acute reactions was done as in RTOG – acute reaction morbidity criteria .The patient was managed according to the toxicity profile.

At the end of 3 weeks of completion of Induction Chemotherapy, tumour response was assessed by Fibreoptic scopy/Contrast CT Head and neck.

At 6 weeks, 3 months and 6 months after concurrent CTRT, acute and sub-acute reactions were noted and tumour response evaluation was assessed by Fibreoptic scopy/Contrast CT Head and neck.

Statistical Analysis
Data were analyzed using SPSS version 20. Frequency distribution of response and categorical variables were determined. Chi square test for proportions to compare differences between Sequential therapy arm and concurrent chemoradiation arm for site, mucositis, dysphagia, hematological toxicities and tumour response was determined.

Significant figures
Suggestive significance (p value:0.05<p<0.10)
* Moderately significant (p value: 0.01<p<0.05)
** Strongly significant (p value: p<0.01)

RESULTS
20 patients with T1N+, T2/T3 any N stages of Carcinoma Hypopharynx were for the prospective arm (ICT + CTRT). 20 patients treated with CTRT previously were included in the control arm. The patients were selected according to the inclusion and exclusion criteria as mentioned earlier. 20 patients treated with Sequential therapy (ICT + CTRT) served as cases under Arm A. The other 20 patients who underwent Concurrent chemoradiation alone served as controls under Arm B**.** During and at the completion of treatment, patients were evaluated for tumour response, mucositis, neutropenia, anemia, and thrombocytopenia. After completion of the treatment, the patients were put on regular follow up. Patients were evaluated for tumor response and dysphagia at 6 weeks, 3 months and 6 months post treatment completion.

In the present study of forty patients of T1N+, T2/T3 any N stages of Carcinoma Hypopharynx, the various characteristics are shown in the following pages.

Characteristics		**Arm A n (%)**	**Arm B n (%)**
Subjects		20	20
Age(mean ±SD)		50.6±9.433	52.8± 6.429
Sex	Male	15(75%)	18(90%)
	Female	5(25%)	2(10%)

Table 2: The patient and tumor characteristics are summarized.

Site	**Arm A n (%)**	**Arm B n (%)**
Pyriform Fossa	15(75%)	16(80%)
Posterior Pharyngeal Wall	1(5%)	2(10%)
Post Cricoid region	4(20%)	2(10%)

Response assessment post Induction Chemotherapy (ICT)
Out of twenty patients in Arm A, on tumour response assessment 3 weeks after 2 cycles of induction chemotherapy

- Partial response was observed in 15 (75%) patients
- Complete response was observed in 3 (15%) patients
- Stable disease was present in 2 (10%) patients.
- Progressive disease (PD) was not observed in any of the patients.

Table 3: Response assessment post Induction chemotherapy.

	Tumor Response	**n(%)**
Post ICT	Stable Disease	2(10%)
	Partial Response	15(75%)
	Complete Response	3(15%)

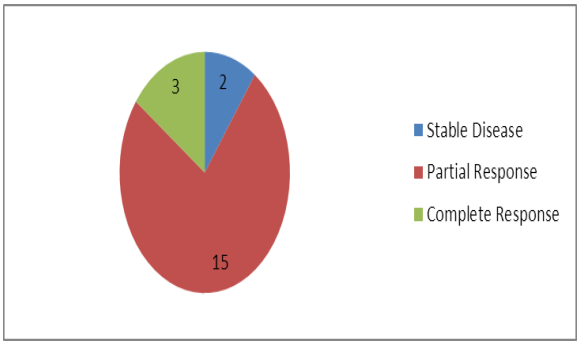

Fig 1: Pie chart showing Response assessment post Induction chemotherapy.

Mucositis and dysphagia

In the present study, we assessed various grades of mucositis and dysphagia during treatment and following RT in all patients.

Dysphagia

All patients in our study had nasogastric tube inserted before the start of radiotherapy to avoid complications, and the nasogastic tube was removed after completion of treatment, thus dysphagia assessment was done 6 weeks, 3 months and 6 months after completion of treatment.

In case study (ICT + CTRT) arm

At 6 weeks after treatment - Grade I and II dysphagia was seen in 11 (61.1%), and 7 (38.9%) patients respectively.

At 3 months after treatment- Grade 0, 1 and 2 dysphagia was seen in 0 (0%), 16 (88.9%), and 2 (11.1%) patients respectively.

At 6 months after treatment- Grade 0 and 1 dysphagia was seen in 13 (72.2%) and 5 (27.8%) patients respectively

In control study (CTRT) arm

- At 6 weeks after treatment - Grade I and II dysphagia was seen in10 (55%), and 9 (45%) patients respectively.
- At 3 months after treatment- Grade 0, 1 and 2 dysphagia was seen in1 (5%), 14 (70%), and 5 (25%) patients respectively.
- At 6 months after treatment- Grade 0 and 1 dysphagia was seen in 11(61.1%) and 7 (38.9%) patients respectively.

Table 4: Mucositis Analysis and dysphagia analysis.

		Grade	Arm A n (%)	Arm B n (%)	p-value
Mucositis	Week 3	Grade 1	15 (78.9%)	18 (90%)	0.33
		Grade 2	4 (21.1%)	2 (10%)	
	Week 7	Grade 2	12(66.7%)	16 (80%)	0.35
		Grade 3	6(33.3%)	4 (20%)	
Dysphagia	6 months post treatment	No dysphagia	13(72.2%)	11(61.6%)	0.48
		Grade 1	5(27.8%)	7(38.9%)	

Hematological toxicities

In our study we assessed for grade III - IV of neutropenia, anaemia and thrombocytopenia during treatment.

Case study (ICT + CTRT) arm

- Neutropenia (Grade III – IV) – 6 (33.3%) patients
- Anemia (Grade III – IV) - 2 (11.1%) patients
- Thrombocytopenia (Grade III – IV) – 1 (5.6%) patients

Control study (CTRT) arm

- Neutropenia (Grade III – IV) – 4 (20%)patients
- Anemia (Grade III – IV) - 2 (10%) patients
- Thrombocytopenia (Grade III – IV) – 1 (5%) patients

Table 5: Hematological toxicity analysis.

Hematological toxicities		Arm A n (%)	Arm B n (%)	p-value
Grade III-IV	Neutropenia	6(33.3%)	4(20%)	0.35
	Anemia	2(11.1%)	2(10%)	0.91
	Thrombocytopenia	1(5.6%)	1(5%)	0.93

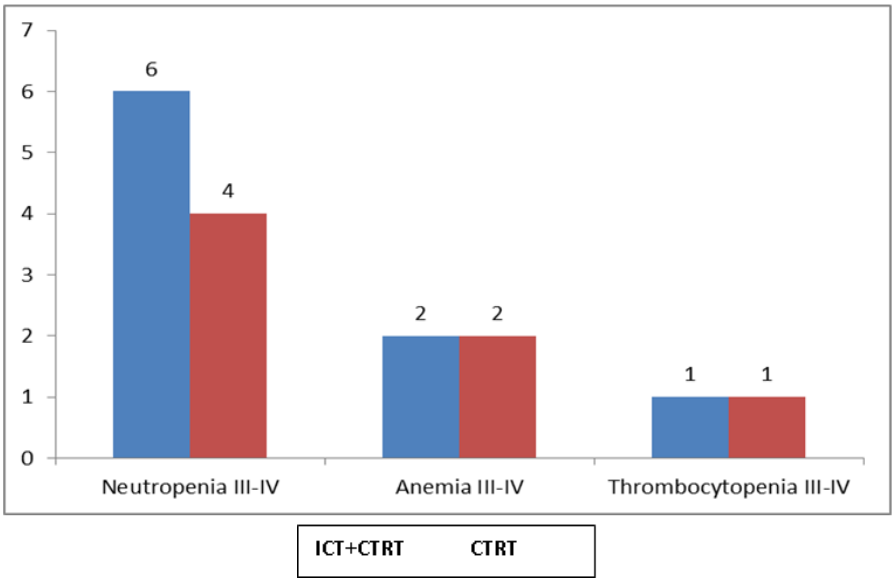

Fig 2: Bar chart showing Hematological toxicities Analysis Grade III-IV.

Tumour Response

Tumour response was assessed and compared 6 weeks, 3 months and 6 months after completion of treatment. The following are the observations seen:

In the case study (ICT + CTRT) arm

- At 6 weeks after treatment – PR and CR was seen in 8 (44.4%) and 10 (55.6%) patients respectively.
- At 3 months after treatment – PR and CR was seen in 5 (27.8%), and 13 (72.2%) patients respectively.
- At 6 months after treatment – PR and CR was seen in 2 (11.1%) and 16 (88.9%) patients respectively.

None of the patients included in the Sequential therapy arm developed Stable disease or Progressive disease on assessment of tumour response.

In the control study (CTRT) arm

- At 6 weeks after treatment – SD, PR and CR was seen in 2 (10%), 11 (55%) and 7 (35%) patients respectively.
- At 3 months after treatment – PD, PR and CR was seen in 2 (10%), 8 (40%) and 10 (50%) patients respectively.
- At 6 months after treatment – PR and CR was seen in 6 (33.3%) and 12 (66.7%) patients respectively.

Table-6: Tumour Response Analysis (6 months post treatment)

Tumor Response		Arm A n(%)	Arm B n(%)	P value
6 Months Post Treatment	Partial Response	2 (11.1%)	2 (11.1%)	0.10
	Complete Response	16 (88.9%)	12 (66.7%)	

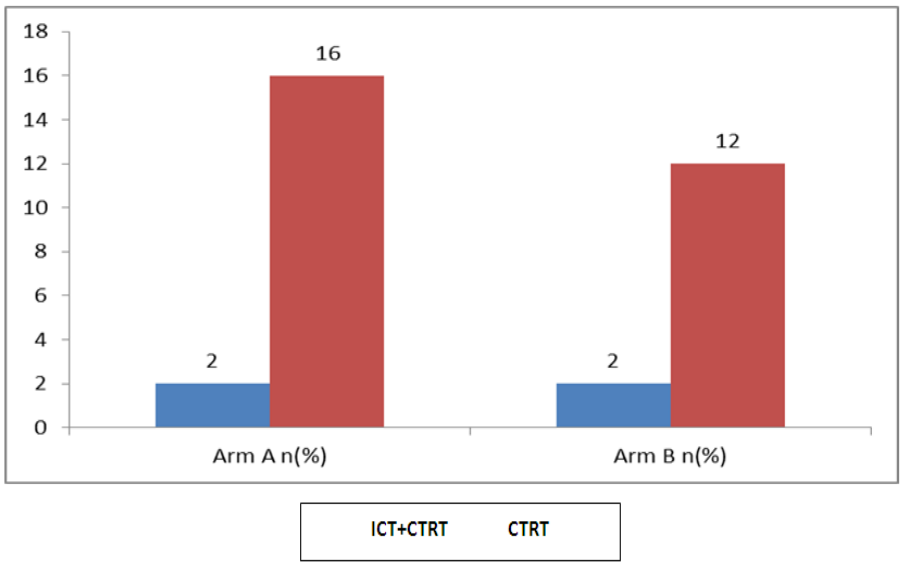

Fig 3: Bar chart showing tumor response 6 months post treatment.

DISCUSSION

A total of 40 patients with T1N+, T2/T3 any N, M0 stages of Carcinoma Hypopharynx were included in the study. The 20 patients who underwent Sequential therapy (Induction chemotherapy followed by chemoradiation) served as cases. In this arm, the patients received two cycles of three weekly Induction chemotherapy of two drugs, PACLITAXEL (175mg/m^2) and CISPLATIN (70mg/m^2). This was followed by response assessment 3 weeks after the 2nd cycle of ICT. Patients with complete response received definitive radiation alone and patients with less than complete response received chemoradiation with two cycles of concurrent three weekly CISPLATIN (70 mg/m^2).

Radiation was given for a total dose of 7000 cGy, 200cGy per fraction, 5 days per week (Mon- Fri) over a period of 7 weeks.20 patients who were taken up for concurrent chemoradiation served as controls. Patients here received chemoradiation with two cycles of concurrent three weekly CISPLATIN (70 mg/m^2). Radiation was given for a total dose of 7000 cGy, 200 cGy per fraction, 5 days per week (Mon- Fri) over a period of 7 weeks.

This study was conducted to compare the loco-regional response and patterns of failure in carcinoma hypopharynx patients treated with induction chemotherapy followed by chemoradiation versus chemoradiation alone and to assess and compare the toxicity profile in patients treated with induction chemotherapy followed by chemoradiation versus chemoradiation alone. All the patients were graded for mucositis, dysphagia, and hematological toxicities. The tumour response at 6 weeks, 3 months and 6months post treatment in all patients were assessed and documented. In addition the tumour response 3 weeks post ICT in patients who received the same was also documented. Treatment completion was seen in 18 patients (90%) in Arm A and in all 20 patients (100%) in Arm B. Out of twenty patients in Arm A, 3 weeks after 2 cycles of induction chemotherapy, partial response was observed in 15 (75%) patients, complete response was observed in 3 (15%) patients and stable disease was present in 2 (10%) patients.

The incidence of grade III mucositis was highest in both the arms at the 7th week of radiation. Grade III mucositis was seen in 6 (33.3%) patients in Arm A and in 4 (20%) patients in Arm B at 7th week of radiation but the difference was not statistically significant. The incidence was in accordance with which it occurred in a study by C.Barone et al.,[14] that showed grade III mucositis in 23% of patients who received sequential therapy. From our study, we found that incidence of severity of mucositis was near to equal in both case and control group during the course of treatment (3rd -7th week). Mucosa subsequently healed by 1 month after end of treatment in all patients and remained healthy at 3 months follow up also.

Neutropenia (Grade III/IV) developed in 6 (33.3%) patients in Arm A and 4 (20%) patients in Arm B respectively. We found that there was no significant difference in number of patients having grade III/IV hematological toxicities in both the groups.

All patients in our study had nasogastric tube inserted before the start of radiotherapy to avoid complications, and the nasogastric tube was removed after completion of treatment, thus dysphagia assessment was done 6 weeks, 3 months and 6 months after completion of treatment. From our study, we found that incidence and severity of dysphagia was highest at 6 weeks after treatment, Grade II dysphagia was seen in 7 (38.9%) patients in Arm A against 9 (45%) patients in Arm B. This is much less than the incidence reported in the study by Barone et al., which showed incidence of grade 3 and 4 dysphagia to be 65%. The lower incidence of dysphagia in our study may be attributed to the usage of nasogastric tube for feeding from the start of radiotherapy. On comparing the two groups with respect to dysphagia, both groups had minimal difference but patients treated with sequential therapy had slightly lesser patients with higher grades of dysphagia, though the p values were not significant.

After 6 weeks post treatment – PR and CR was seen in 8 (44.4%) and 10 (55.6%) patients respectively in the ICT+CTRT arm whereas SD, PR and CR was seen in 2 (10%), 11 (55%) and 7 (35%) patients respectively in the CTRT arm. After 3 months post treatment – PR and CR was seen in 5 (27.8%), and 13 (72.2%) patients respectively in the ICT+CTRT arm whereas PD, PR and CR was seen in 2 (10%), 8 (40%) and 10 (50%) patients respectively in the CTRT arm. At 6 months post treatment – PR and CR was seen in 2 (11.1%) and 16 (88.9%) patients respectively in the ICT+CTRT arm whereas PR and CR was seen in 6 (33.3%) and 12 (66.7%) patients respectively in the CTRT arm. The proportion of complete responders at 6 weeks follow up in Arm A were in accordance to the results in a study by A.Pacagnella et al.[15] in which patients who received Sequential therapy were associated with CR of 50% against CR 21.3% in patients treated with CT/RT alone. The results were also in accordance with those obtained in a study by N.Somani et al.,[16] which yielded CR of 66.63% and PR of 22.72% at the end of treatment in patients treated with sequential therapy. We found that on comparing the two groups with respect to tumour response, "p value" was not statistically significant though it was close to being suggestive of significance at 6 weeks and 3 months follow up, and comparison showed increased number of patients with complete response in the ICT+CTRT arm at 6 weeks and 3 months follow up.

More importantly the "p value" was suggestive of significance at 6 months follow up and the Sequential therapy (ICT + CTRT) arm showed increased number of patients with complete response when compared to the

patients who received concurrent CTRT alone. It was also observed that none of the patients in the ICT + CTRT arm developed progressive disease at the end of 6 months post treatment completion as opposed to 2 (10%) patients in the CTRT alone arm. Hence we may infer that the addition of ICT to concurrent CTRT did not increase mucositis, hematological toxicities and dysphagia as compared to patients treated with concurrent CTRT alone. Thereby sequential therapy did not have had a role in increasing the incidence, preponing the onset & elevating the severity of toxicities in patients when compared to patients treated with CTRT alone. ICT+CTRT was generally well tolerated and offered a safe and effective means of management in T1N+, T2/T3 any N, M0 stages of Carcinoma Hypopharynx patients. The increasing body of preclinical and clinical data justifies the use of ICT+CTRT in order to provide improved therapeutic efficacy. Although our study consisted of a small number of patients, it has shown favorable improvement in tumour response rates and reduced treatment failure while not affecting the toxicity profile for patients both during and after RT. Hence we recommend the usage of sequential therapy (ICT+CTRT) in T1N+, T2/T3 any N, M0 stages of Carcinoma Hypopharynx patients.

CONCLUSION

Sequential therapy (ICT+CTRT) improved complete response rates (88.9% vs 66.7% at 6 months) in T1N+, T2/T3 any N, M0 stages of Carcinoma Hypopharynx patients when compared to concurrent chemoradiation alone (CTRT). This implied the better locoregional response and reduced failure rates in patients treated with sequential therapy which may translate into better disease free survival and overall survival in the future. Long term follow up data is needed to confirm these findings and also sequential therapy did not increase the toxicity profile of patients when compared to patients treated with CTRT alone.

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CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or Publication of this article.

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