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To find out the toxicity profile of concomitant boost radiotherapy over concurrent chemoradiation in locally advanced head and neck cancer

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Abstract

Background: Evidence of head and neck malignancies has been found in ancient skulls. The oldest known tumour is contained in a fossil found in East Africa by Leakey that dates back more than 500,000 years

Methods: This prospective randomized study was conducted in the Department of Radiation Therapy & Oncology, Regional Cancer Centre, IGMC, Shimla and patients were enrolled for a period of one year, from July 2012 to July 2013.It included all the eligible, previously untreated patients of squamous cell carcinoma of Head and Neck with histologically confirmed diagnosis and no evidence of distant metastasis. The sites included were oro-pharynx, hypo-pharynx and larynx with stages III, IV A and IV B.

Results: Skin toxicities ranging from G1 to G4 were seen in both the arms during treatment. Most of the patients suffered from G3 toxicity which was comparable in both the arms (*51.4% vs 48.6% p=0.813*). Grade 4 toxicity was slightly higher in Concomitant CRT arm but difference was not statistically significant *(21.6% vs 11.4 %, p=0.246).* Combined Grade 3 & 4 toxicity was also more in CRT arm (73% vs 60%) but it was not significant statistically (p=0.066).

Conclusion: Similar local control with better tolerability could be achieved with accelerated six fractions per week radiation therapy compared to concomitant chemoradiation especially in a resource limited country like India

Keywords: Toxicity, Six fraction, Concomitant chemoradiation, Conventional fractionation.

Introduction

Evidence of head and neck malignancies has been found in ancient skulls. The oldest known tumour is contained in a fossil found in East Africa by Leakey that dates back more than 500,000 years.[1]

The term *Head and Neck Cancer* is usually taken to cover the range of malignant neoplasms that develop in the oral cavity, nasal cavity, paranasal sinuses, pharynx, larynx and salivary glands.

Most head and neck cancers, indeed 95% or more, are squamous cell carcinomas (SCC) and variants thereof, originating from the epithelium of the mucosal lining of the upper aerodigestive tract (UADT), and adenocarcinomas from associated secretory glands.[2-3]

As the patients who usually present in our OPDs are of low socioeconomic status with poor general condition and thus impaired tolerability to chemoradiation, we thought of considering an alternative method, better than conventional radiotherapy alone but comparable to concomitant chemoradiation in terms of disease control. Since, it seems plausible to compare accelerated radiotherapy with standard chemoradiation, this study was planned. In this study we decreased overall treatment time, thereby taking care of accelerated repopulation of malignant cells and compared the toxicities and disease response of this approach with concomitant chemoradiation, which is the standard of care in developed countries for locally advanced head and neck carcinoma.

The addition of concomitant chemotherapy to standard radiation and accelerated fractionation radiotherapy are the two methods to potentiate the effect of radiation on cancers of head & neck. Many trials have evaluated these two strategies but a search on PubMed indicated that there has been no trial which directly compared accelerated six fractions per week radiation and chemoradiotherapy (using standard fractionation and weekly cisplatin) in SCCHN. Hence, to our knowledge the study conducted in our institute is the first trial which has done a head to head comparison of both of these treatment strategies in locally advanced head and neck cancers.

This trial has compared the two modalities to see whether the same or near to the same local control and tolerability be achieved with accelerated radiotherapy vis-à-vis concomitant chemoradiation, particularly for Indian population.

Material and Methods

This prospective randomized study was conducted in the Department of Radiation Therapy & Oncology, Regional Cancer Centre, IGMC, Shimla and patients were enrolled for a period of one year, from July 2012 to July 2013.It included all the eligible, previously untreated patients of squamous cell carcinoma of Head and Neck with histologically confirmed diagnosis and no evidence of distant metastasis. The sites included were oro-pharynx, hypo-pharynx and larynx with stages III, IV A and IV B.

Inclusion Criteria

- Age ≤ 70yrs.
- Sites – oropharynx, hypopharynx, larynx.
- Histology – squamous cell carcinoma.
- Stages – III , IV A , IV B.
- Previously untreated patients.
- Hb> 10gm%.
- Pretreatment leucocyte count of > 4000/cu mm.
- Platelet count > 100,000/cu mm.
- Normal renal function test.
- Karnofsky performance status > 70.

Exclusion Criteria

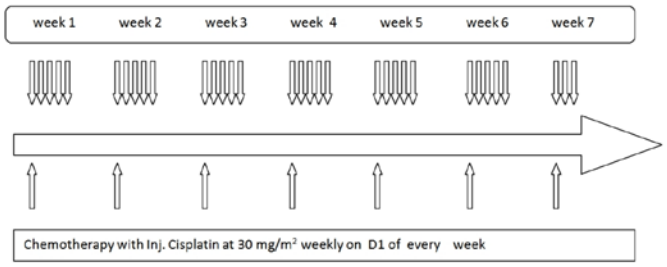
- Histology other than squamous cell carcinoma.
- Sites other than oropharynx, hypopharynx, and larynx
- Age > 70yrs.
- Deranged RFT / LFT.
- Karnofsky performance status < 70.
- Distant metastasis (Stage IV C).

Randomization

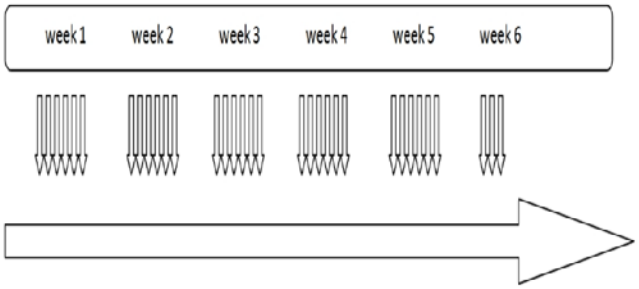
Randomization was carried out by stratified randomization technique. The treatment assignment was stratified according to clinical stages of disease. Patients were randomized into two group's one study and control group based on treatment they received. Approximately equal numbers were assigned to each group.

Study Design

Control arm (CRT arm): Patients were subjected to standard concomitant chemoradiotherapy. Patients assigned to CRT arm were given radiation as one fraction (2Gy) per day, on five consecutive days from Monday to Friday (TOTAL: 66Gy/6½wks/33#)along with intravenous Cisplatin 30 mg/m^2 weekly (on Mondays) for seven doses.



Study arm (AFRT arm): Patients assigned to AFRT arm underwent radiation therapy as one fraction (2Gy) per day for 6 days from Monday to Saturday. If any unintended interruption of the treatment occurred, missing treatment was given as soon as possible, preferably within a week. The total dose and number of fractions were the same as in control arm but treatment duration was reduced by one week (TOTAL:66Gy/5½wks/33#).



Administration of Treatment

External beam radiation therapy was given by teletherapy *Theratron 780E* and *Equinox Cobalt-60* machines using two parallel-opposed fields or three fields by "shrinking-field" technique. Orfit cast was used for immobilization in all the patients. Initially the radiation portals encompassed primary disease, involved lymph nodes and potential microscopic disease around primary and in clinically uninvolved lymph nodes. In most of the cases whole neck along with primary disease was included in the initial radiation portals. After 44Gy/22#, the posterior neck field was reduced to spare spinal cord. After the microscopic disease had received 50Gy/25#, the field was reduced to include involved lymph node region with one level up. After 60Gy the field was reduced to include involved primary sites with primary echelon and involved lymph nodes.

Skin reactions were carefully monitored during radiotherapy and ointments of epidermal growth factor stimulant, topical antibiotics and in case of superadded infection systemic antibiotics were administered.

For mucositis, frequent oral rinses and gargles with benzydamine and chlorhexidine were started from the very beginning of the treatment and topical anaesthetics, analgesics and antifungals were given as

and when required. A course of systemic antifungals or antibiotics was given if needed.

For dysphagia and odynophagia due to pharyngeal toxicity, topical anaesthetics, non-narcotic and narcotic analgesics as per WHO step ladder were given.

Nutritional status, dehydration and other signs and symptoms due to poor oral intake were carefully watched and intravenous fluids to correct dehydration and nutritional support (multivitamins and protein supplements) were given to patients of both arms who developed moderate to severe dysphagia and odynophagia. Nasogastric tube feeding was given to maintain adequate nutrition if necessary.

Patients who developed persistent hoarseness, cough, whispered speech and pain due to laryngeal toxicity were carefully monitored and were given antitussives, analgesics and/or steroids.

For dryness of mouth, patients were instructed to have frequent oral sips of water. Consultation from other departments was taken as and when required and for the management of co-morbid conditions.

Assessment of status and toxicity:-

Assessment for toxicity was done at every week during treatment and at the end of treatment. Toxicity was assessed according to the RTOG (Radiation Therapy Oncology Group) toxicity criteria (Appendix – V). The scores are based on the patient's subjective symptoms, objective examination findings and treatment of the symptoms.

At first follow-up after treatment, toxicity status and loco-regional disease status of all the patients was recorded.

The response was considered to be complete if there was complete regression of disease with no visible or palpable disease, partial if there was more than 50% regression in the lesion in maximal diameter, stable if lesion regressed less than 50% in maximal diameter and progressive if lesion increased by 25% or appearance of new lesion or secondary metastatic disease.

Follow – up

Six weeks after completion of treatment first follow-up was done. History was taken and a thorough clinical examination in particular, neck examination, oral examination and indirect laryngoscopic examination for disease status and for toxicity status was performed. Confirmation of indirect laryngoscopy findings, loco-regional disease status and toxicity status was also done in ENT Department at first follow up and subsequent follow ups every two months. If required direct laryngoscopic examination or other investigations like Barium swallow x-ray, CT scan, x-ray chest were advised to the patients during follow up. Side effects of treatment that occurred within 90 days of start of radiotherapy were considered acute effects and those occurring or persisting more than 90 days after the start of radiotherapy were considered late effects.

Patients who had recurrence or persistent disease were considered for salvage surgery if feasible. Palliative chemotherapy was administered in patients in whom surgery was not feasible.

Statistical analysis

The recorded scores of acute radiation reactions experienced by patients in both the arms were analyzed and compared. The locoregional disease status of the patients in both the arms at the end of radiotherapy and at subsequent follow up was analyzed and compared. The frequency of late toxicity and other parameters were also analyzed and compared. The data was analyzed using Chi-square and t-test and p-values were calculated. IBM SPSS Statistics software version 20 was used for analyzing the data. A *p-value* of < 0.05 was considered statistically significant.

Observations and Results

This study was conducted in the Department of Radiation therapy and Oncology, Regional Cancer Centre, IGMC, Shimla on eligible patients with locally advanced head and neck cancer of stages III, IVA and IVB from July, 2012 to July, 2013. The patients underwent all relevant investigations and staging. Based upon the clinical stage patients were randomized by stratification into the study or control group.

Age of the patients ranged between 40 to 70 years with median age of presentation being 57.47 years. Most of the patients were in the 51-60 yrs age group. Both the arms were balanced with regards to age distribution. 66 patients (91.7%) were males and 6 patients (8.3%) were females. In the Accelerated RT arm, out of 35 patients, 32 patients (91.4%) were males and 3 patients (8.6%) were females. In the Concomitant CRT arm, out of 37 patients, 34 patients (91.9%) were males, and 3 patients (8.1%) were females.

Observation No : 1

Skin Toxicities Observed During Radiotherapy

Skin Toxicity during Treatment * Rx Arm Crosstabulation

P = 0.391			Rx Arm		Total	P value
			CRT	ART		
Skin Toxicity during Treatment	G1	Number	4	3	7	0.748
		% within Rx Arm	10.8%	8.6%	9.7%	
	G2	Number	6	11	17	0.128
		% within Rx Arm	16.2%	31.4%	23.6%	
	G3	Number	19	17	36	0.813
		% within Rx Arm	51.4%	48.6%	50.0%	
	G4	Number	8	4	12	0.246
		% within Rx Arm	21.6%	11.4%	16.7%	
Total		Number	37	35	72	
		% within Rx Arm	100.0%	100.0%	100.0%	

Skin toxicities ranging from G1 to G4 were seen in both the arms during treatment. Most of the patients suffered from G3 toxicity which was comparable in both the arms (*51.4% vs 48.6% p=0.813*). Grade 4 toxicity was slightly higher in Concomitant CRT arm but difference was not statistically significant *(21.6% vs 11.4 %, p=0.246).* Combined Grade 3 & 4 toxicity was also more in CRT arm (73% vs 60%) but it was not significant statistically (p=0.066).

Observation No : 2

Mucositis During Radiotherapy

Mucosal Toxicity during Treatment * Rx Arm Crosstabulation

P = 0.371			Rx Arm		Total	P value
			CRT	ART		
Mucosal Toxicity during Treatment	G2	Number	15	20	35	0.159
		% within Rx Arm	40.5%	57.1%	48.6%	
	G3	Number	19	13	32	0.225
		% within Rx Arm	51.4%	37.1%	44.4%	
	G4	Number	3	2	5	0.689
		% within Rx Arm	8.1%	5.7%	6.9%	
Total		Number	37	35	72	
		% within Rx Arm	100.0%	100.0%	100.0%	

Mucositis was seen in both the arms during treatment. Majority of patients developed grade 2 toxicity i.e. patchy mucositis with moderate pain requiring analgesia. In Accelerated RT arm 57.1% patients and in Concomitant CRT arm 40.5% patients developed grade 2 mucositis (p=0.159). Grade 3 toxicity was higher in the Concomitant CRT group as compared to Accelerated RT group but difference was not statistically significant. (51.4*% vs. 37.1%, p=0.225*). Grade 3 & 4 toxicities when combined were higher in CRT arm (59.5%vs 42.8%) but without statistical significance (p=0.159).

Observation No: 3

Laryngeal Toxicity during Radiotherapy

Laryngeal Toxicity during Treatment * Rx Arm Crosstabulation

P = 0.289			Rx Arm		Total	P value
			CRT	ART		
Laryngeal Toxicity during Treatment	G0	Number	6	9	15	0.321
		% within Rx Arm	16.2%	25.7%	20.8%	
	G1	Number	15	17	32	0.493
		% within Rx Arm	40.5%	48.6%	44.4%	
	G2	Number	14	9	23	0.271
		% within Rx Arm	37.8%	25.7%	31.9%	
	G3	Number	2	0	2	0.163
		% within Rx Arm	5.4%	0.0%	2.8%	
Total		Number	37	35	72	
		% within Rx Arm	100.0%	100.0%	100.0%	

Mild or intermittent hoarseness and cough not requiring antitussives i.e. G1 laryngeal toxicity was seen in majority (n=32, 44.4 %) of patients. The number of patients who experienced Grade2 and Grade3 laryngeal toxicity was higher in Concomitant CRT arm as compared to Accelerated arm but difference was not statistically significant(p = 0.271 & 0.163 respectively). All these toxicities were transient and were managed conservatively.

Observation No : 4

Pharyngeal Toxicity During Radiotherapy

Pharyngeal Toxicity during Treatment * Rx Arm Crosstabulation

P = 0.244			Rx Arm		Total	P value
			CRT	ART		
Pharyngeal Toxicity during Treatment	G0	Number	0	1	1	0.302
		% within Rx Arm	0.0%	2.9%	1.4%	
	G1	Number	12	18	30	0.102
		% within Rx Arm	32.4%	51.4%	41.7%	
	G2	Number	18	12	30	0.217
		% within Rx Arm	48.6%	34.3%	41.7%	
	G3	Number	7	4	11	0.377
		% within Rx Arm	18.9%	11.4%	15.3%	
Total		Number	37	35	72	
		% within Rx Arm	100.0%	100.0%	100.0%	

Grade 1 & 2 pharyngeal toxicities were more commonly seen in patients of both the arms. The G1 pharyngeal toxicities were higher in the Accelerated RT arm(51.4%) as compared to the Concomitant CRT arm (32.4%) whereas G2 & G3 pharyngeal toxicities were higher in Concomitant CRT arm (67.5%) as compared to Accelerated RT arm(45.7%) *(p =0.061).*

All these toxicities were transient and were managed conservatively.

Observation No: 5

Haematological Toxicity

Hematological Toxicity duringTreatment * Rx Arm Crosstabulation

P = 0.012			Rx Arm		Total	P value
			CRT	ART		
Hematological Toxicity during Treatment	G0	Number	25	34	59	0.001
		% within Rx Arm	67.6%	97.1%	81.9%	
	G1	Number	1	0	1	0.327
		% within Rx Arm	2.7%	0.0%	1.4%	
	G2	Number	5	0	5	0.024
		% within Rx Arm	13.5%	0.0%	6.9%	
	G3	Number	6	1	7	0.055
		% within Rx Arm	16.2%	2.9%	9.7%	
Total		Number	37	35	72	
		% within Rx Arm	100.0%	100.0%	100.0%	

G2 & G3 haematological toxicities were significantly (combined p value = 0.002) higher in the concomitant CRT arm (32.4%) as compared to Accelerated RT arm

(2.9%). Only one patient in accelerated arm had any hematological toxicity.

Discussion

For a period of one year, from July, 2012 to July, 2013 seventy nine patients were enrolled and 72 patients completed the assigned treatment in two arms, 35 in accelerated RT arm and 37 in Concomitant CRT arm. The distribution of patient and tumor characteristics (like age, sex, smoking habits, alcohol consumption, dietary habits, site and stage of disease) was comparable in the two groups. Majority of patients in accelerated arm completed treatment in stipulated period of 5½ weeks without any interruption. Median overall time for completion of treatment was 38 days and 45 days in accelerated RT arm and Concomitant CRT arm respectively. Among the patients in the accelerated RT arm 5.7% (2 patients) had treatment interruption whereas in the Concomitant CRT arm 16.2% (6 patients) had treatment interruption mainly due to pharyngeal, mucosal, cutaneous and hematological toxicities. The treatment interruptions were higher in CRT arm but these were not statistically significant.

Higher severe acute reactions (grade 3 & 4 cutaneous & mucosal toxicities) were seen in the Concomitant CRT arm due to combined effect of chemotherapy and conventional radiotherapy with accumulated dose per week (AD) of 10 Gy. Patients in Accelerated RT arm were also expected to have higher acute reactions due to accumulated dose per week (AD) of 12 Gy as acute toxicity is directly dependent on accumulated dose per week.

Most of the patients had Grade 3 skin toxicity (confluent moist desquamation) during treatment. Combined grade 3 and grade 4 toxicity was higher in concomitant CRT arm(73%) compared to ART arm(60%) . However the difference was not statistically significant (p = 0.066).These were managed with topical applications of epidermal growth factor ointment, oral antibiotics and systemic antibiotics if needed.

It was seen that during radiation treatment confluent fibrinous mucositis with pain (Grade 3 acute mucosal toxicity) was seen more in the Concomitant CRT arm (51.4%) as compared to accelerated RT arm (37.1%). Grade 3 & 4 toxicities when combined were again higher in CRT arm(59.5% vs 42.8%) but difference was not statistically significant (p=0.159). This severe mucositis was managed conservatively with frequent oral rinses and gargles, local anaesthetics, antifungals and analgesics. The mucositis subsided in most of the patients at first follow-up.

G2 & G3 laryngeal toxicity (persistent hoarseness or whispered speech with throat pain and cough) was seen in higher number of patients in the Concomitant CRT arm. In the accelerated RT arm 25.7% patients and in Concomitant CRT arm 43.2% patients experienced G2 to G3 acute laryngeal toxicity (p=0.118). This was also managed conservatively with non narcotics and narcotic analgesics, antitussives, steroids and antibiotics.

Significantly higher haematological toxicity was observed in the concomitant CRT arm in 32.4 % of patients as compared to 2.9% in accelerated RT arm and was statistically significant (p=0.001). It was expected because of myelosuppression caused by cisplatin.

Delayed healing of confluent mucositis and skin reactions was observed in the both the arms. In the accelerated RT arm 2.9% skin reactions and 5.8% mucositis as compared to 8.1% skin reactions and 0% mucositis in concomitant CRT arm were still healing

even after six weeks of completion of radiation therapy at first follow-up. However this difference was not statistically significant. All acute toxicities in patients of both the arms were completely healed after 8 weeks of completion of treatment and at second follow-up.

The incidence of confluent mucositis (37.1%) in ART arm in this study is lower than that observed in combined analysis of DAHANCA 6 & 7 trials (55%)[4]. However it is comparable to that seen in DAHANCA 6 (40%) and is higher than that of IAEA-ACC study (10%).The overall incidence of grade 3 and higher of all the acute toxicities in our study is 65.7% (23/35) in ART arm.

Acute radiation related morbidity in concomitant CRT arm in the present study is slightly lower to concomitant CRT arm of Intergroup trial by Aldelstein et al.[5] Overall Grade 3 or worse toxicity occurred in 85% in concomitant CRT arm in this trial while in present study the corresponding figure is 81.08 % (30/37)

Conclusion

Similar local control with better tolerability could be achieved with accelerated six fractions per week radiation therapy compared to concomitant chemoradiation especially in a resource limited country like India.

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