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TO COMPARE THE EFFICACY OF CONCOMITANT BOOST RADIOTHERAPY AGAINST CONCURRENT CHEMORADIATION IN LOCALLY ADVANCED HEAD AND NECK CANCER (OROPHARYNX/LARYNX/ HYPOPHARYNX)

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Abstract

Background: 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.

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: On first follow up, overall there was complete response at nodal site in 50 patients(69.4%) 26 in CRT arm (70.3%) and 24 in ART arm(68.6%), however the difference was not statistically significant (p=0.875).

Conclusion: There was comparable locoregional disease control with the use of accelerated six fractions a week radiation therapy compared to concomitant chemoradiation with conventional fractionation.

Keywords: Six fraction, Concomitant chemoradiation, Conventional fractionation.

Introduction

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.

Head and neck malignancies constitute 6% of all the cancers worldwide. In India according to National Cancer Registry Programme (ICMR), squamous cell carcinomas of head and neck region account for 29.6% of all cancers in males (range 24.3% - 34.3%) and 11.84% of all cancers in females (range 10.5 % - 15.5%) in different hospital registries in India[1].

Concomitant chemoradiation represents a more attractive strategy because some chemotherapeutic agents radiosensitize tumor cells and also provide additive cytotoxicity. The superiority of this type of nonsurgical strategy relative to RT alone has been demonstrated in randomized trials in squamous cell carcinoma of other anatomic sites including the esophagus and uterine cervix.[2-4]

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.

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:-

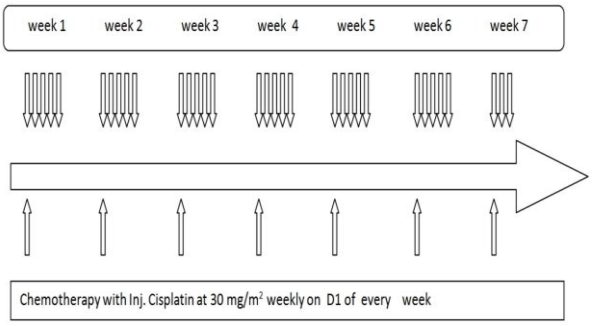
- Histology other than squamous cell carcinoma.
- Sites other than oropharynx, hypopharynx, and larynx.
- Age > 70yrs.
- Deranged RFT / LFT.
- Karnofsky performance status < 70.
- Distant metastasis (Stage IV C).

RANDOMIZATION:

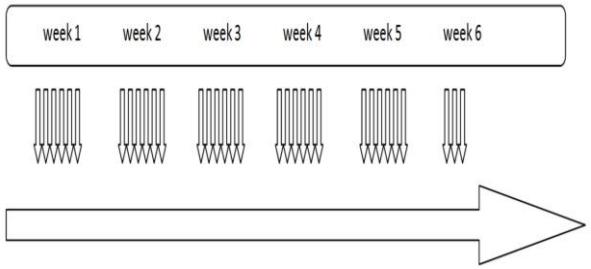
Randomization was carried out by stratified randomization technique. The treatment assignment was stratified according to clinical stages of disease. Patients were randomized into two group's one study and control group based on treatment they received. Approximately equal numbers were assigned to each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

PRIMARY DISEASE ON FIRST FOLLOW-UP

Local Disease Response First Follow-up * Rx Arm Cross tabulation

P = 0.840			Rx Arm		Total	P value
			CRT	ART		
Local Disease Response First Follow-up	Complete Response	Number	31	27	58	0.476
		% within Rx Arm	83.8%	77.1%	80.6%	
	Partial Response	Number	2	3	5	0.597
		% within Rx Arm	5.4%	8.6%	6.9%	
	Stable Disease	Number	2	2	4	0.954
		% within Rx Arm	5.4%	5.7%	5.6%	
	Progressive Disease	Number	0	1	1	0.302
		% within Rx Arm	0.0%	2.9%	1.4%	
	NA	Number	2	2	4	0.954
		% within Rx Arm	5.4%	5.7%	5.6%	
Total		Number	37	35	72	
		% within Rx Arm	100.0%	100.0%	100.0%	

Two patients from Accelerated arm and two patients from Concomitant CRT arm were lost to follow up. On first follow up, overall 58 patients (80.6%) were with no evidence of disease at primary site, 5 patients (6.9 %) were having partial response at the primary site. In the Accelerated RT arm, 27 patients (77.1%) were with no evidence of disease and 3 patients (8.6%) were having partial response at the primary site. In the Concomitant CRT arm 31 patients (83.8%) were with no evidence of disease and 2 patients (5.4%) were having partial response at the primary site.Two patients in each of the arms had stable disease. Only one patient had progressive disease who was in accelerated RT arm. **There was no statistically significant difference in the disease response at primary site in both the arms (p = 0.840).**

OBSERVATION NO: 2

NODAL RESPONSE AT FIRST FOLLOW-UP

Nodal Disease Response First Follow-up * Arm * N - Stage Crosstabulation

N - Stage				Arm		Total	P value
				CRT	ART		
N0	Nodal Disease Response First Follow-up	Node Negative	Number	5	3	8	
			% within Arm	100.0%	100.0%	100.0%	
	Total		Number	5	3	8	
			% within Arm	100.0%	100.0%	100.0%	
N1	Nodal Disease Response First Follow-up	Complete Response	Number	14	10	24	0.469
			% within Arm	82.4%	71.4%	77.4%	
		No C.R.	Number	1	3	4	0.199
			% within Arm	5.9%	21.4%	12.9%	
		NA	Number	2	1	3	0.664
			% within Arm	11.8%	7.1%	9.7%	
	Total		Number	17	14	31	0.422
			% within Arm	100.0%	100.0%	100.0%	
N2	Nodal Disease Response First Follow-up	Complete Response	Number	12	14	26	0.568
			% within Arm	85.7%	77.8%	81.2%	
		No C.R.	Number	2	3	5	0.854
			% within Arm	14.3%	16.7%	15.6%	
		NA	Number	0	1	1	0.372
			% within Arm	0.0%	5.6%	3.1%	
	Total		Number	14	18	32	0.648
			% within Arm	100.0%	100.0%	100.0%	
N3	Nodal Disease Response First Follow-up	No C.R.	Number	1		1	
			% within Arm	100.0%		100.0%	
	Total		Number	1		1	
			% within Arm	100.0%		100.0%	
Total	Nodal Disease Response First Follow-up	Complete Response	Number	26	24	50	0.875
			% within Arm	70.3%	68.6%	69.4%	

	No C.R.	Number	4	6	10	0.437
		% within Arm	10.8%	17.1%	13.9%	
	Node Negative	Number	5	3	8	0.504
		% within Arm	13.5%	8.6%	11.1%	
	NA	Number	2	2	4	0.954
		% within Arm	5.4%	5.7%	5.6%	
Total		Number	37	35	72	0.819
		% within Arm	100.0%	100.0%	100.0%	

On first follow up, overall there was complete response at nodal site in 50 patients(69.4%) 26 in CRT arm (70.3%) and 24 in ART arm(68.6%), however the difference was not statistically significant (p=0.875).

OBSERVATION NO: 3

LOCOREGIONAL DISEASE STATUS AT MEDIAN FOLLOW-UP

Disease Response at Median Follow-up * Rx Arm Crosstabulation

P = 0.442			Rx Arm		Total	P value
			CRT	ART		
Disease Response at Median Follow-up	Complete Response	Number	29	25	54	0.496
		% within Rx Arm	78.4%	71.4%	75.0%	
	Partial Response	Number	3	5	8	0.404
		% within Rx Arm	8.1%	14.3%	11.1%	
	Stable Disease	Number	3	1	4	0.331
		% within Rx Arm	8.1%	2.9%	5.6%	
	Progressive Disease	Number	0	2	2	0.151
		% within Rx Arm	0.0%	5.7%	2.8%	
	NA	Number	2	2	4	0.954
		% within Rx Arm	5.4%	5.7%	5.6%	
Total		Number	37	35	72	
		% within Rx Arm	100.0%	100.0%	100.0%	

Median follow-up period was 4.5 months. Complete response (CR) was seen in 71.4% in the Accelerated RT arm compared to 78.4% in the Concomitant CRT arm. Partial response (PR) was observed in 14.3% of patients in the Accelerated RT arm compared to 8.1% in the Concomitant CRT arm. Stable diseae (SD) was observed in 2.9% patients in the Accelerated RT arm, compared to 8.1% patients in the Concomitant CRT arm. Progressive disease was noted in 5.7% patients in the Accelerated RT arm compared to 0% patients in the Concomitant CRT arm. **The 7% difference in CR of locoregional disease was not statistically significant (p=0.496).**

OBSERVATION NO: 4

DISEASE RESPONSE: SEX WISE

TREATMENT GROUP CROSS TABULATION

Sex			Arm		Total	P value
			CRT	ART		
Male	Disease Response	Complete	27	23	50	**0.335**
			79.4%	71.9%	75.8%	
		No C.R.	7	9	16	
			20.6%	28.1%	24.2%	
	Total		34	32	66	
Female	Disease Response	Complete	2	2	4	**0.800**
			66.7%	66.7%	66.7%	
		No C.R.	1	1	2	
			33.3%	33.3%	33.3%	
	Total		3	3	6	

No statistically significant difference was found in CR in both the arms in males as well as in females.

Discussion

Regarding loco regional response to radiotherapy in our study we observed comparable local control at primary site in both the arms with statistically non significant difference at nodal sites was present. On first follow-up 77.1% had complete response at primary site and 68.6% had complete response at nodal site in accelerated arm and in concomitant CRT arm the corresponding figures are 83.8% and 70.3% respectively.
The median follow up period was 4.5 months. In accelerated RT arm 71.4% patients and in concomitant CRT arm 78.4% patients had no evidence of disease (CR) at median follow-up. This difference is not statistically significant and reflects near to same result with accelerated radiotherapy.

Therefore, in terms of radiobiology, accelerated six fractions per week radiation therapy by shortening overall treatment time minimises tumour repopulation during treatment and therefore increase the probability of tumour control for a similar total dose. The acute toxicity is higher than that of conventional fractionation but is comparable (or slightly less) to that of concomitant CRT.

In DAHANCA and IAEA-ACC study the five year actuarial locoregional control was 70% and 42% respectively in the accelerated RT arm. In RTOG 91-11 trial the 2 year locoregional control was 78% in the concomitant CRT arm. Though our study is small the locoregional control observed in our study is in accordance with that of accelerated arm of DAHANCA trial and concomitant arm of RTOG 91-11 trial (71.4 & 78.4 respectively).

Hence, based on our study (though it is small), DAHANCA trial and IAEA-ACC study it is apparent that accelerated six fractions per week treatment is an attractive alternative to concomitant CRT, especially in countries with six days a week working schedule. It is also clear from the present study that accelerated RT results into similar locoregional control of the disease as with concomitant CRT which is standard of care for locally advanced head and neck cancers. Overall acute and late toxicities were observed to be less in the accelerated RT arm as compared to concomitant CRT arm (although not statistically significant).

Therefore it can be said that, same or near to the same local control and tolerability can be achieved with accelerated radiotherapy vis-à-vis concomitant chemoradiation, particularly for Indian population. Moreover the turnover on the machine would be much faster with the use of accelerated fractionation and this in turn would reduce patient waiting list. Accelerated RT can also be used as standard therapy in situations which preclude the use of concomitant chemotherapy.

Conclusion

There was comparable locoregional disease control with the use of accelerated six fractions a week radiation therapy compared to concomitant chemoradiation with conventional fractionation.

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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