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To compare the disease response and loco-regional tumor control of accelerated radiation (six fractions per week) versus concomitant chemoradiation with conventional fractionation (five fractions per week) in locally advanced head and neck cancer

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Abstract

Background: 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.

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: 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 that was in accelerated RT arm.

Conclusion: 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: Six fraction, chemoradiation, Local control.

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.

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.

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].

Head and neck cancer is the sixth most common type of cancer and accounting for an estimated 650,000 new cases and 350,000 cancer deaths worldwide every year[2]. Nearly 60% of this population present with locally advanced, but non-metastatic disease. Locoregional failure constitutes the predominant recurrence pattern with most fatality resulting from uncontrolled local and / or regional disease[2].

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.

Pre-Treatment Work-UP

A complete history was recorded and thorough physical examination was performed including local examination of disease, neck examinations, indirect and direct larynogoscopy followed by cytology and biopsy (if not done previously). Baseline investigations like complete blood count, blood biochemistry, urine routine and microscopic examination were ordered in all the patients. All the patients were sent for dental checkup before radiotherapy and in patients who underwent any invasive dental procedure as a part of pre-RT dental prophylaxis, a minimum gap of 2 weeks was maintained between the procedure and start of radiation therapy.

Radiographic examination included x-rays of chest and soft tissue neck. CECT scan of head and neck was also done in all the patients. The patients were staged as per AJCC Cancer Staging Manual, seventh edition (2010) (Appendix VII & VIII). A signed informed consent was obtained from all patients.

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

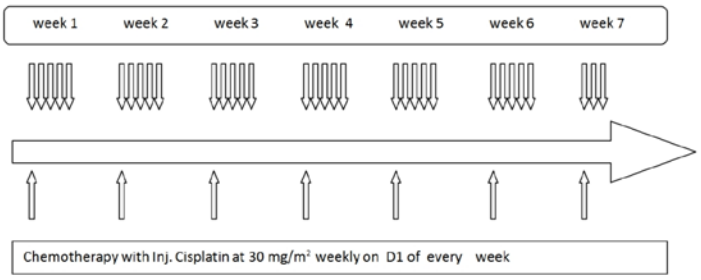
- Histology other than squamous cell carcinoma.
- Sites other than oropharynx, hypopharynx, and larynx
- Age > 70yrs
- Deranged RFT / LFT.
- Karnofsky performance status < 70.
- Distant metastasis (Stage IV C).

Randomization

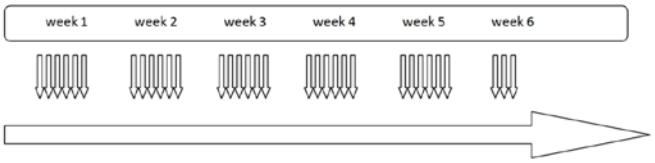
Randomization was carried out by stratified randomization technique. The treatment assignment was stratified according to clinical stages of disease. Patients were randomized into two group's one study and control group based on treatment they received. Approximately equal numbers were assigned to each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

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

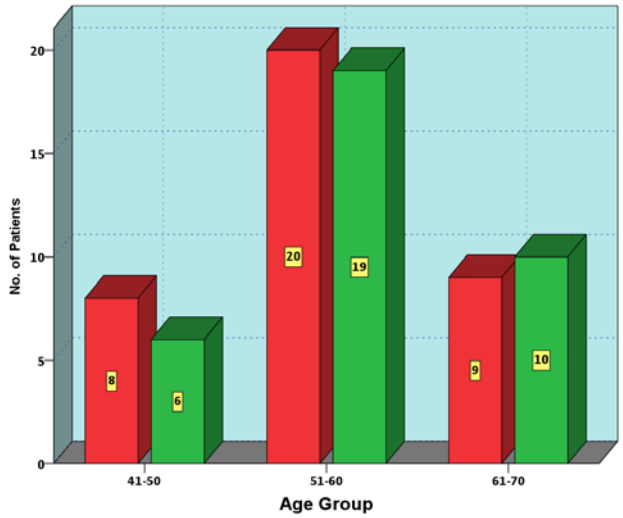
This study was conducted in the Department of Radiation therapy and Oncology, Regional Cancer Centre, IGMC, Shimla on eligible patients with locally advanced head and neck cancer of stages III, IVA and IVB from July, 2012 to July, 2013. The patients

underwent all relevant investigations and staging. Based upon the clinical stage patients were randomized by stratification into the study or control group.

Over 200 patients were assessed for eligibility and 79 of them were enrolled.

Of the 79 patients, 39 patients were randomized to study arm i.e. accelerated six fractions a week radiotherapy and 40 patients were randomized to the control arm i.e. radiotherapy with concomitant weekly Cisplatin. Seven patients did not receive the allocated treatment. Four patients were non-compliant/defaulted during treatment and three received off-protocol treatment (two due to development of secondaries and one due to early progression of disease). Thirty five (35) patients completed treatment in the study group (ART) and thirty seven (37) patients completed treatment in the control group (CRT). So, a total of seventy two (72) patients received allocated treatment and were analyzed. The response to treatment and toxicities was monitored, recorded and analyzed in all the patients.

Age Distribution



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.

Sex Distribution

P = 0.943			Rx Arm		Total	P value
			CRT	ART		
Sex	Male	Number	34	32	66	0.943
		% within Rx Arm	91.9%	91.4%	91.7%	
	Female	Number	3	3	6	0.943
		% within Rx Arm	8.1%	8.6%	8.3%	
Total		Number	37	35	72	
		% within Rx Arm	100.0%	100.0%	100.0%	

Out of 72 patients, 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.

Site Wise Distribution

Site * Rx Arm Crosstabulation

P = 0.710			Rx Arm		Total	P value
			CRT	ART		
Site	Oropharynx	Number	18	19	37	0.632
		% within Rx Arm	48.6%	54.3%	51.4%	
	Larynx	Number	16	12	28	0.435
		% within Rx Arm	43.2%	34.3%	38.9%	
	Hypopharynx	Number	3	4	7	0.634
		% within Rx Arm	8.1%	11.4%	9.7%	
Total		Number	37	35	72	
		% within Rx Arm	100.0%	100.0%	100.0%	

Most of the patients had disease in oropharynx i.e. 37 patients (51.4%) followed by larynx, i.e. 28 patients (38.9%) and 7 patients (9.7%) had disease in the hypopharynx. In the Accelerated RT arm, out of 35 patients, 19 patients (48.4%) were ca oropharynx cases,

12 patients (34.3%) were of ca larynx and 4 patients (11.4 %) were ca hypopharynx patients.In the Concomitant CRT arm, out of 37 patients, 18 patients (48.6%) were ca oropharynx cases, 16 patients (43.2%) were ca larynx cases and 3 patients (8.1%) were ca hypopharynx cases. Both the arms were well balanced.

Stage Wise Distribution

Stage Grouping * Rx Arm Crosstabulation

P = 0.422			Rx Arm		Total	P value
			CRT	ART		
Stage Grouping	III	Number	16	12	28	0.435
		% within Rx Arm	43.2%	34.3%	38.9%	
	IVA	Number	20	23	43	0.315
		% within Rx Arm	54.1%	65.7%	59.7%	
	IVB	Number	1	0	1	0.327
		% within Rx Arm	2.7%	0.0%	1.4%	
Total		Number	37	35	72	
		% within Rx Arm	100.0%	100.0%	100.0%	

Both arms in our study were balanced with regard to the stage of the disease. Most of the patients were in stage III and IVA of disease.

Primary Disease on First Follow-UP

Local Disease Response First Follow-up * Rx Arm Crosstabulation

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).

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	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

	Follow-up		% 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).

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).

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.

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).

However we observed higher acute toxicities (particularly G3 & 4 skin toxicity) and more treatment interruptions in concomitant CRT arm.

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 reduction of overall treatment time by one week (from 6 ½weeks to 5 ½ weeks) which minimizes the accelerated tumor repopulation and therefore increases tumor control probability. This shortening of treatment time increased the turnover on machine and thus reduced waiting period for patients. Therefore in a busy department like ours which caters to large number of cancer patients particularly from far off places of Himachal Pradesh, accelerated fractionation RT would be more logistic as it would reduce patient's visit/stay in hospital by one week. Moreover, there would be optimum resource utilization as we have a six day workweek. 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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