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TO COMPARE THE TOXICITY PROFILE OF ACCELERATED RADIOTHERAPY (SIX FRACTIONS PER WEEK) WITH CONCOMITANT CHEMO-RADIOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK CANCER

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Abstract
Background: Head and neck malignancies are common among males in India. The age adjusted incidence rate of head and neck cancer in India in males is 16.4/100,000 and in females it is 8.8/100,000.In All India Institute of Medical Science head and neck cancer represents 25% of all malignancies registered
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: Grade 3 and grade 4 skin toxicities were higher in CRT arm but without statistically significant difference from that in ART arm. G3 & G4 mucositis was higher in the Concomitant CRT arm however the difference was not statistically significant. G2 and G3 Laryngeal Toxicities were higher in Concomitant CRT arm as compared to Accelerated arm but the difference was not statistically significant. 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.
Conclusion: Higher peak incidence of toxicities was seen in concomitant CRT arm as compared to accelerated arm.
Keywords: Toxocity, six fraction, chemoradiation, Local control

Introduction

Head and neck malignancies are common among males in India. The age adjusted incidence rate of head and neck cancer in India in males is 16.4/100,000 and in females it is 8.8/100,000[1].In All India Institute of Medical Science head and neck cancer represents 25% of all malignancies registered.

In Regional Cancer Centre, Indira Gandhi Medical College, Shimla Head and Neck cancers represented 16% of all cancers registered from 2001 to 2010. Over this period these represented 10.6% of all cancers in males and 5.4% of all female cancers. In the year 2012, there were 316 new patients of head & neck cancers in RCC Shimla which constituted 16.37 % of all the newly registered patients(1930). The geographic distribution reveals very large variation in different countries and regions with low incidence reported in Western Europe and high incidence in South Asia, parts of Africa and South America.[2]

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.

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:

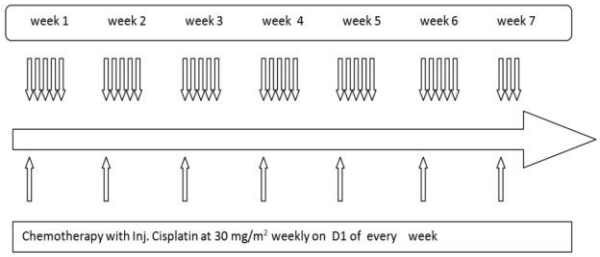
- Histology other than squamous cell carcinoma.
- Sites other than oropharynx, hypopharynx, and larynx.
- Age > 70yrs.
- Deranged RFT / LFT.
- Karnofsky performance status < 70.
- Distant metastasis (Stage IV C).

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.

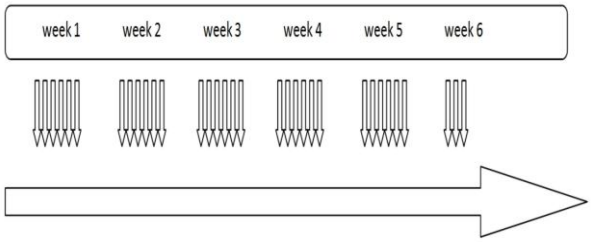
STUDY DESIGN:

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.

Table 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).

Table 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).

Table 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.

Table 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.

Table 5: ACUTE SALIVARY GLAND TOXICITY

Acute Salivary Gland Toxicity * Rx Arm Crosstabulation						
P = 0.814			Rx Arm		Total	P value
			CRT	ART		
Salivary Gland Toxicity	G0	Number	22	20	42	0.842
		% within Rx Arm	59.5%	57.1%	58.3%	
	G1	Number	13	14	27	0.670
		% within Rx Arm	35.1%	40.0%	37.5%	
	G2	Number	2	1	3	0.954
		% within Rx Arm	5.4%	2.9%	4.2%	
Total		Number	37	35	72	
		% within Rx Arm	100.0%	100.0%	100.0%	

Salivary gland toxicities ranging from grade 0 to grade 2 were seen in both the arms. Both the arms showed similar acute salivary gland toxicity.

Table 6: 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.

Moderate to severe dysphagia or odynophagia requiring semisolid or liquid diet and narcotic analgesics with intravenous fluids and nutritional supplementation (G2-G3 pharyngeal toxicity) was seen in more number of patients in the concomitant CRT arm (67.5% vs 45.7% ;p=0.061).

More number of patients in concomitant chemoradiotherapy arm required nasogastric tube feeding (18.9% vs 11.4%, p = 0.377).

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%)[3]. 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.[4] 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).

Regarding late toxicities in our study, we observed radiation induced late morbidity in the form of xerostomia and subcutaneous fibrosis at anterior aspect of neck, which did not differ significantly in both groups. In the accelerated arm patients, we observed that subcutaneous fibrosis at the anterior aspect of neck was present in 22.9% of patients and it was present in 24.3% patients in the concomitant CRT arm. The difference was not statistically significant.

In the DAHANCA trial and recently published IAEA-ACC too, the probability of developing a severe late radiation related complication mainly in the form of late cutaneous fibrosis, mucosal atrophy or necrosis did not differ significantly between the conventional and accelerated (six fractions per week) radiation therapy.

CONCLUSION

Higher peak incidence of toxicities was seen in concomitant CRT arm as compared to accelerated arm.

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