PURE HYPERFRACTIONATED RADIOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK CANCERS- A RANDOMISED CONTROL STUDY

R. Giridharan¹, N. V. Kalaiyarasi²

¹Professor, Department of Radiation Oncology, RGGGH, Madras Medical College, Chennai.

²Professor and HOD, Department of Radiation Oncology, RGGGH, Madras Medical College, Chennai.

ABSTRACT

BACKGROUND

Around 40,000 patients are newly diagnosed annually with squamous cell carcinoma of head & neck worldwide. About 60% of the patients presenting with locally advanced disease show poor response to conventional treatment. Loco regional failure constitutes the predominant recurrence pattern. Hence it is imperative to design the therapeutic schedules to improve the outcome in this group.

Aims of the Study- 1. To evaluate the efficacy of hyperfractionated radiotherapy in locally advanced head and neck cancer with stage III and IV A excluding T4a lesions involving bone or cartilage. 2. To determine the differences in immediate tumour response between conventional and hyperfractionated radiotherapy. 3. To compare the toxicity between conventional and hyperfractionated radiotherapy.

MATERIALS AND METHODS

A randomised controlled study consisting of 45 patients with locally advanced squamous cell carcinoma head and neck stage III and IVA who presented to our OPD from march 2004 to October 2004 where randomised into Study arm (hyperfractionation)-22 patients and Control Arm (conventional fractionation)-23 patients.

Patients in study arm were treated with 120 cGy per fraction 2 fractions per day in 6 hour interval^[1] to a total dose of 76.8 Gy and in control arm were treated with 200 cGy per fraction single fraction per day to a total dose of 66 Gy using Teletherapy cobalt 60 unit.

RESULTS

18 patients in study arm (81%) and 7 patients in control arm (31%) achieved complete response. Nearly 70% of patients in control arm had partial response. This is statistically significant with $P=0.002$. Grade II skin toxicity was seen equally in both arms. Grade III skin reactions were seen only in study arm (13%).

CONCLUSION

1. Hyperfractionation radiotherapy produced significant better immediate complete response compared to conventional fractionation radiotherapy in locally advanced head and neck squamous cell carcinoma. 2. Toxicity is more in hyperfractionation regime compared to conventional fractionation but can be effectively managed.

KEYWORDS

Radiotherapy, Head and Neck Cancer, Hyperfractionated Radiotherapy, Oncology.

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BACKGROUND

Around 40,000 patients are newly diagnosed annually with squamous cell carcinoma of head & neck worldwide. About 60% of the patients present with locally advanced but non-metastatic state. Loco regional failure constitutes the predominant recurrence pattern & most fatalities result from uncontrolled loco regional disease. Patients with locally advanced disease show poor response to standard treatment comprising surgery and conventional radiotherapy regime. Hence it is imperative to design therapeutic schedules to improve the outcome in this group.

Aim of the Study

1. To evaluate the efficacy of hyperfractionated radiotherapy in locally advanced head and neck cancer with stage III and IV A excluding T4a lesions involving bone or cartilage.
2. To determine the differences in immediate tumour response between conventional and hyperfractionated radiotherapy.
3. To compare the toxicity between conventional and hyperfractionated radiotherapy.

MATERIALS AND METHODS

A randomised control study.

Total Number of Patients.

Study arm – 22.

Control arm – 23.

Study Period- March 2004 to October 2004.

Inclusion Criteria

1. Locally advanced stage III and IV A.
2. Histopathological documentation of squamous cell carcinoma in primary.

Financial or Other, Competing Interest: None.

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Corresponding Author:

Dr. R. Giridharan,

Professor,

Department of Radiation Oncology,

RGGGH, Madras Medical College,

Chennai.

E-mail: gknila@gmail.com

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3. Informed consent.
4. Age >18 years.
5. Performance status >70 (KPS).
6. Haemoglobin >10 gms%.
7. No evidence of distant metastasis.

Exclusion Criteria

1. Nasopharyngeal and paranasal sinus carcinoma.
2. T4a lesion involving bone and cartilage.
3. Patient with N3 stage.
4. KPS <70.
5. Histology other than squamous cell carcinoma.
6. Previously treated patients.

Eligible patients were randomised alternatively into both arms in 1:1 ratio based on computed permuted blocks to reduce selection bias.

	ARM 1– Study ARM	ARM 2– Control ARM
Total Dose	7680 cGy	6600 cGy
Dose Per Fraction	120 cGy	200 cGy
No. of Fractions Per Day	2 at 6 Hour Interval	1
Treatment Duration	6.2 Weeks	6.3 Weeks
Treatment Schedule	Monday to Friday 5 Days a Week	Monday to Friday 5 Days a Week
Treatment Protocol		

Radiotherapy Planning

Positioning: Supine

Treatment Delivery: External beam using cobalt 60 teletherapy unit

Treatment Volume

Study ARM 1

1. Initial target volume: Primary tumour+ 2 cm margin, with involved and draining lymph nodes.
2. Spinal cord excluded after 4320 cGy.
3. After 5520 cGy only primary tumour and involved lymph nodes were treated up to 7680 cGy.

Control ARM 2

1. Initial target volume: Primary tumour+ 2 cm margin, with involved and draining lymph nodes.
2. Spinal cord excluded after 4000 cGy.
3. After 4000 cGy only primary tumour and involved lymph nodes were treated up to 6600 cGy.

Treatment Portal- Opposing Lateral

Patients were reviewed every day and at the weekend by clinical examination for tumour response and acute reactions. At the completion of RT and after 6 weeks, patients were assessed for tumour response and acute reactions by-

1. Indirect and Direct Laryngoscopy.
2. Ba Swallow.
3. CT Scan in necessary cases.

Tumour Response

Response was graded as following-

Complete Response- Defined as complete disappearance of all clinical and radiological evidence of disease i.e, (100%).

Partial Response- Defined as any response less than complete response is (50-99%).

Static Response- Defined as any response with Tumour shrinkage less than 50% but no progression.

Progressive Response- Defined as greater than 25% increase in initial size or the appearance of new lesion or metastatic disease.

Acute Reactions

Grade 0- No reaction.

Grade I- Erythema.

Grade II- Patchy mucositis.

Grade III- Confluent Mucositis.

Grade IV- Ulceration.

Skin Reactions

Grade 0- No changes over baseline.

Grade I- Follicular faint erythema, epilation, dry desquamation, reduced sweating.

Grade II- Tender bright erythema, patchy moist desquamation, moderate oedema.

Grade III- Confluent moist desquamation other than skin fold pitting oedema.

Grade IV- Ulceration, haemorrhage, necrosis.

Follow Up

First follow-up after 6 weeks after completion of radiotherapy.

Monthly follow-up for 1 year and 3 monthly thereafter.

Statistical Methods

1. The distribution of cases by the study and control arm with respect to factors and variables studied were presented using descriptive statistics.
2. The difference in proportion of cases between study and control groups of factors measured on a nominal scale were tested for statistical significance using chi-square test. Yate's correction was employed.
3. Fischer's exact probability test was used whenever zero frequencies are encountered.
4. Student-t test is used whenever the factors studied are measured on interval scale.
5. Odds ratio was employed to study the extent of complete response achieved in the study group compared to control group.

RESULTS

Total No. of Patients.

Study arm- 22 and Control arm- 23. All the patients completed the treatment and were included for analysis. (Table 1).

	Study ARM	Control ARM
Male	17	17
Female	5	6
Total	22	23
Table 1		

Distribution by Age

Distribution of age were identical in study arm and control arm.

Age range was 39-40 years in the study arm and 30-60 years in the control arm.

This is not statistically significant. (Chart 1).

Chart 1

Distribution by Gender

In both the study and control arm, majority were male nearly 75% in control arm and 77% in study arm, consistent with other epidemiological studies (Chart 2).

Chart 2

Habits

The distribution of patients according to risk stratification was not statistically significant (p=0.42) (Table 2).

Habits	Study ARM		Control ARM	
	Yes	No	Yes	No
Smoking ^[2]	6	16	16	7
Smoking and Alcohol	10	12	13	10
Tobacco Chewing	6	16	7	16

Table 2

Distribution of the Cases by Site

In the study arm, there was a preponderance of oral cavity cancers, while control arm had equal proportion of distribution among each site. The distribution was statistically not significant p=0.77(Chart 3).

Chart 3

Distribution by Tumour Size

Majority of the lesions were T3 and above in both arms. P value not significant p=0.41 (chart 4)

Chart 4

Distribution by Nodal Stage

Nodal distribution between the two groups did not have any statistical significance p=0.3(chart 5).

Chart 5

Distribution by Stage

Both arms had nearly equal distribution of both the stage III and stage IV A p=0.87(chart 6).

Chart 6

Distribution by Tumour Differentiation

Moderately differentiated cancers formed the majority group in both the arms (Chart 7).

Chart 7

Response of the Study

Distribution of Cases by Response to Treatment

Chart 8

18 patients in study arm (81%) and 7 patients in control arm (31%) achieved complete response.

Nearly 70% in control arm had partial response. (Chart 8).

This is statistically significant.

Treatment Outcome

$\chi^2 = 10.56$ $P = 0.002$ (Highly Significant).

Odds Ratio = 9.02.

Response to Treatment by Sex

P value was not significant ($p=0.2$) between response among males and females (Table 3).

Gender	Study ARM		Control ARM	
	Complete Response	Partial Response	Complete Response	Partial Response
Male	14	3	5	12
Female	4	1	2	4

Table 3

Response to Treatment by Age

P value was significant ($p=0.03$) for age less than 50 years and above 50 years with age above 50 years having a better outcome (Table 4).

Age	Study ARM		Control ARM	
	Complete Response	Partial Response	Complete Response	Partial Response
< 50 Years	4	4	6	11
> 50 Years	14	0	1	5

Table 4

Response by Site Distribution

Overall outcome by site did not have statistically significant values with worst outcome for oral cavity tumours in the study group ($p=0.007$) (Chart 9).

Chart 9

Response to Treatment by Stage

Complete response was statistically significant with regard to stage of disease ($p=0.002$) (Chart 10).

Chart 10

Response by Tumour differentiation

Complete response was statistically significant with $P=0.002$.

Moderately differentiated tumours in study arm had significantly better response (chart 11).

Chart 11

T Size	Study Arm		Control ARM	
	Complete Response	Partial Response	Complete Response	Partial Response
T2	4	2	4	6
T3,4	14	2	3	10

Table 5. Response to treatment by tumour size $P=0.002$

Nodal Stage	Study ARM		Control ARM	
	Complete Response	Partial Response	Complete Response	Partial Response
N0	2	0	4	6
N1	10	1	2	4
N2	6	3	1	6

Table 6. Response by nodal status $P=0.003$

Acute Reaction

Skin reactions (RTOG) Grade II was seen in 86% of patients in study arm and Grade III was seen in 13% of study arm. No patients had grade IV toxicity (Table 7).

Mucosal reactions Grade II was seen in half patients and Grade III in remaining half patients. No patients had Grade IV toxicity (Table 8).

Skin Toxicity	Study ARM	Control ARM
Grade 2	19	21
Grade 3	3	0

Table 7

Mucosal Toxicity	Study ARM	Control ARM
Grade 2	11	21
Grade 3	11	2

Table 8

DISCUSSION

Immediate Loco regional control rates of head and neck cancer can be improved by pure Hyperfractionation in comparison to conventional fractionation.^[3]

Pure Hyperfractionation is characterised by

1. Smaller dose per fraction in comparison to conventional fractionation^[4]

2. At least the same or a moderately increased total dose in comparison to conventional fractionation
3. About the same overall treatment time, cumulative dose per week should be kept constant same as in conventional fractionation

Rationale for this Strategy are

1. Increased opportunity for tumour cell redistribution and re-oxygenation between dose fractions,
2. Possibly low oxygen enhancement ratio with small incremental dose.
3. Differential sparing of late reacting normal tissues with small dose fractions.

The RTOG studied hyper fractionated RT for patients with stage III AND IV head and neck squamous cell carcinoma. Patients were randomized to 70 Gy in 35 fractions treated once daily or hyper fractionated RT with 120 cGy twice daily. hyper fractionation^[5] was shown to improve the local control rate compared with conventional fractionation. Similar results were obtained in meta-analysis of following randomised hyper fractionated trials: EORTC 2279 trial, Barcelona trial, Rioderjenero trial, New Delhi trial, Toronto Trial.

In Our study achieved immediate complete response was achieved in 81% of patients in the study arm and 31% in control arm. The outcome was statistically significant $P=0.002$.

The difference between the response among males & females was not statistical significant.

Patients with age >50 yrs. had better complete response than patients with age < 50 yrs.

The distribution of tumour according to site wise and the final response did not have any statistically significance.

Increase in stage of tumour was associated with poor outcome in our study which was statistically significant in both study group and control group.

Moderately differentiated tumours had better clinical response than well or poorly differentiated types.

Increasing T stage and N stage was associated with inferior outcome as larger tumours tend to be hypoxic and less radiosensitive.

Karen et al in their analysis of RTOG 9003^[6] for prognostic parameters pointed out that only N stage, T stage and radiation fractionation remain the best significant independent prognostic indicators. Our study also mirrored their findings.

CONCLUSION

1. Hyperfractionation radiotherapy produced significant better immediate complete response compared to conventional fractionation radiotherapy in locally advanced head and neck squamous cell carcinoma^[7].
2. Toxicity is more in hyperfractionation regime compared to conventional fractionation but can be effectively managed.^[8]
3. Further studies are needed to determine whether chemical and biological modifiers further improve the outcome of altered fractionation radiotherapy.^{[9][10]}

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