COMPARISON OF HYPERFRACTIONATION AND CONVENTIONAL METHOD OF RADIOTHERAPY IN HEAD AND NECK CANCERS

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ABSTRACT

BACKGROUND

Head and Neck cancers are conventionally treated with either radical surgery or radiotherapy with curative intent in early stages. In advanced stages, larger doses of radiotherapy is required to achieve cure which requires altered fractionation schedules of radiotherapy like hyperfractionation. This study is conducted to assess the response to hyperfractionation radiotherapy in advanced head and neck cancers.

The objective of this study is to compare the Hyperfractionation and Conventional fractionation of Radiotherapy in advanced Head and Neck cancers.

Design- Randomised Controlled Study.

MATERIALS AND METHODS

60 patients with advanced head and neck cancers attending Govt. Arignar Anna Cancer Hospital, Kancheepuram, were selected and divided equally into Hyperfractionation Radiotherapy arm and Conventional Radiotherapy arm for 6 weeks and treatment response was evaluated.

RESULTS

In the Hyperfractionation Radiotherapy arm complete response (53%), partial response (37%), minimal response (3%) and stable disease (7%) were noted. In the conventional Radiotherapy arm complete response (30%), partial response (57%), minimal response (7%), stable disease (3%) and tumour progression (3%) were present.

CONCLUSION

Better locoregional control can be obtained with Hyperfractionation radiotherapy than Conventional radiotherapy, though acute toxicities are more common in the former.

KEYWORDS

Head and Neck Cancers, Hyperfractionated Radiotherapy, Conventional Radiotherapy.

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BACKGROUND

Head and neck cancers comprise 4.3% of cancers worldwide and the annual estimate of new cases in India is 181,606 (NCDIR, NCDP, 2013).[1] It occurs predominantly in older population, occurring in males more than in females at all sites. The most common histological type is that of squamous cell carcinoma and is associated with tobacco and tobacco products, 70% - 80% of all cancers in the oral cavity, oropharynx and the larynx in India may be due to smoking or chewing tobacco.[2] Oral and pharynx cancers stand as the third most common cause in males and the fourth common cause in females in developing countries. Oral cancers is a major problem in India and accounts for 50% - 70% of all cancers diagnosed as compared to 2% - 3% in the UK and USA.[3]

Head and neck cancers comprise a heterogeneous group of lesions. Head and neck region has a complex anatomy with four major sites and seventeen subsites, each with its own natural history and patterns of spread. Unlike tumours at other sites, head and neck cancer tends to present with locoregional disease and only 18% - 20% develop distant metastases. Control of the primary site and nodal metastases is of supreme importance and will impact overall survival.[2] At Govt. Arignar Anna Memorial Cancer Institute, Kancheepuram, India, head and neck cancers account for 24% of all new registered cases.

The three modalities of treatment in head and neck malignancies include surgery, chemotherapy and radiotherapy. Out of these modalities, head and neck cancers are mainly treated by surgery and/or RT predominantly.

Large total doses of radiation (65 Gy to 75 Gy) approaching the tolerance of normal tissue are required to eradicate the squamous cell carcinoma arising in the mucosa of head and neck. With conventional fractionation a dose of 55 to 60 Gray in 5 to 6 weeks is considered adequate for microscopic disease, 65 to 70 Grays in 6.5 to 7 weeks is recommended for T1 and T2 tumours, and 75 to 80 Grays is required for T3 and T4 tumours if treated with irradiation alone.[4]

Hyperfractionation is the use of large fractions smaller than standard dose per fraction per day. Hyperfractionation using larger number of dose fractions below 2 Gy is predicted to give a therapeutic gain, especially in advanced tumours

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where a larger tumour dose is required to regress the tumour.[4]

The therapeutic advantages in hyperfractionation is a more rapid increase in tolerance with decreasing dose per fraction for late responding normal tissues than for tumours and increase in long-term local tumour control. It also counteracts repopulation. Hyperfractionation exploits the self-sensitising effect of cell cycle redistribution present in tumour, but absent in late responding normal tissues. Several biologic studies suggest a 6 to 8 hours gap should be allowed between fractions when multiple daily fractions is used to allow maximum repair of normal tissues.[5]

In conventional radiotherapy treatment the commonly used schedule is 2 Gy in a single fraction per day for 5 days a week for 6 - 7 weeks. In hyperfractionation radiotherapy regimen, two to three fractions are delivered each day with a reduced dose per fraction equal to 1.1 - 1.2 Gy. The reduction of the dose per fraction may reduce the amount of late toxicity, despite an increased total dose.[6] Even though both fractions of radiotherapy have been used in the management of advanced head and neck cancers, there is a considerable social and economic problem in doubling the number of treatments. Hyperfractionated radiotherapy requires the patient to wait for six hours within the department in order to complete their treatment on each day of the course lasting for six weeks.[7]

MATERIALS AND METHODS

This non-randomised controlled trial was conducted at Department of Radiation Oncology, Government Arignar Anna Memorial Cancer Hospital, Kancheepuram, for a period of six months from March to August 2000. Sixty patients were selected from those attending the outpatient department of Radiation Oncology. The sample size arrived based on the case input. The study was given approval by the Ethical Committee of the institution. After complete history taking and physical examination the patients underwent baseline investigations including complete blood counts, renal function and liver function tests. Chest x-rays and x-rays of the soft tissues of neck and computed tomography was done if necessary to determine the extent of the lesion. After examination and investigations, histopathological tests were done to determine the type of tumour. All the patients were staged according to the international tumour-node-metastases classification of the American Joint Committee on Cancer.[3]

The Inclusion Criteria included patients presenting with stage III and IV Head and Neck cancers with good performance status, not treated previously with any modality, with biopsy proven squamous cell carcinoma, 30 - 70 years' age group, adequate haemoglobin status above 10 gm/dL and adequate nutritional status.

The Exclusion Criteria included patients with more advanced stage IV presentation such as large skin ulceration, fistula, large fixed N3 metastatic cervical lymph nodes, patients with poor performance status, low haemoglobin percentage and those with distant metastasis.

Sixty patients who fulfilled the inclusion criteria were included in the study. They were given either conventional radiotherapy or hyperfractionation radiotherapy based on the hospital protocol and their willingness to stay in the department for extended hours each day. All the patients were followed up for their clinical response and for complications at the completion of treatment and for six weeks after completion of radiotherapy. Among the sixty patients, thirty patients underwent conventional radiotherapy and the remaining thirty patients underwent hyperfractionation radiotherapy.

Conventional fractionation consists of treatment with single fraction of 2 Gy per day, 5 fractions per week to a total of 60 Gy in 6 weeks through 30 fractions. The hyperfractionation consists of treatment with two fractions per day with a dose of 1.2 Gy per fraction with interfraction interval of 6 hours. All the patients were treated 5 days a week for 6 weeks to a total tumour dose of 72 Gy.

The collected data were analysed with IBM. SPSS statistics software 23.0 version. Demographic parameters were expressed in proportions. The association between the independent variables (clinical parameters) and the dependant variable (complete response) was determined using univariate analysis (chi-square test). The response rate for both modalities of treatment was also arrived. P value less than 0.05 was considered statistically significant.

RESULTS

All the patients treated with hyperfractionation radiotherapy protocol and conventional radiotherapy were evaluated at the end of therapy and six weeks after completion of irradiation treatment. They were evaluated using WHO criteria[8] for response assessment in solid tumours. There were 20 male and 10 female patients in the conventional radiotherapy group and 16 males and 14 females in the hyperfractionation radiotherapy group (Figure 1). In the conventional treatment group, stage III head and neck cancers was diagnosed in 21 (70%) and stage IV in 9 (30%). Whereas in the hyperfractionation group, 14 (47%) had stage III disease and the remaining 16 (53%) had stage IV disease (Figure 2). Regarding the site distribution in the conventional treatment group, 15 (50%) oral cavity, 8 (30%) oropharynx and 6 (20%) had hypopharynx cancers. In the Hyperfractionation group, the site distribution was 17 (57%) oral cavity, 7 (23%) oropharynx, 1 (3%) supraglottic larynx and 5 (17%) hypopharynx malignancies. Analysis of the treatment outcome after the completion of treatment in both groups show that among the patients who underwent conventional treatment, 9 (45%) had complete response in stage III and none had complete response in stage IV (Table 1). In the hyperfractionation therapy group, 15 (83%) in stage III and 2 (18%) in stage IV had complete response. Univariate analysis shows the relative risk or response rate in patients receiving hyperfractionation radiation to be 1.7 times better than the patients receiving conventional fractionation (RR = 1.7) [Table 1]. But the p value and 95% confidence interval were not found to be statistically significant [P= 0.07 95%, CI (0.956 - 3.374)]. Subgroup analysis of the site of lesion and the complete response among both the treatment groups also was not statistically significant (Table 2); 11 (55%) in stage III and 7 (70%) in stage IV had partial response in conventional group. Partial response was observed in 2 (11%) and 7 (63%) in hyperfractionation group in stage III and stage IV respectively. Minimal response was observed in 1 (10%) in conventional treatment group and 1 (9%) in hyperfractionation group and both the patients had stage IV disease. Stable disease without any treatment response was

observed in 2 patients with stage IV disease in the conventional treatment group and 2 patients (1 with stage III and 1 with stage IV disease) in hyperfractionation group.

Some of the common complications, which were observed were mucositis 8 (27%), skin reactions 8 (27%), both skin reactions and mucositis 2 (7%), xerostomia 6 (20%) and odynophagia 2 (7%) in the conventional treatment group (Table 3). In the hyperfractionation treatment group the complications observed were mucositis 14 (47%), skin reactions 16 (53%), both skin reactions and mucositis in 5 (17%), xerostomia 14 (43%), odynophagia 3 (10%) and hoarseness of voice in 1 (3%) of the patients. Toxicities like mucositis and skin reactions are found to be more in the hyperfractionation group than the conventional radiation group.

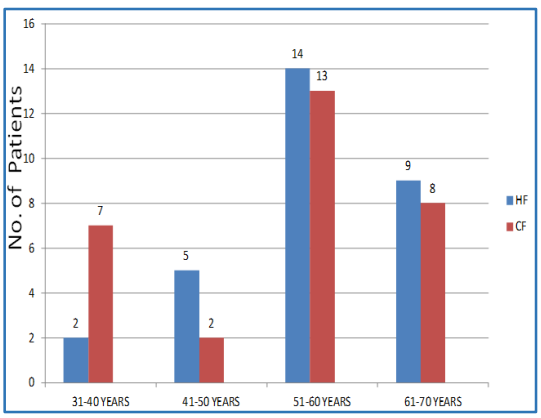

Figure 1. Age Distribution

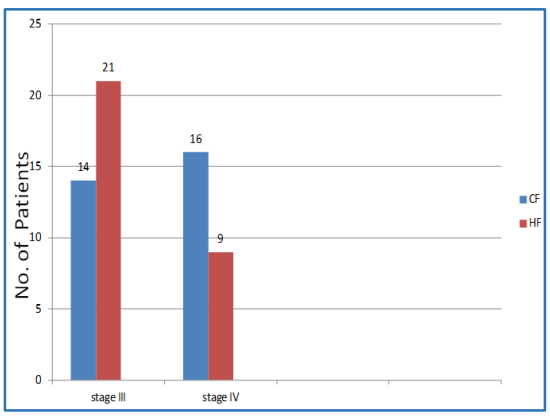

Figure 2. Stage Distribution

Variable	Category	Complete Response Present n (%)	Complete Response Absent n (%)	P Value	Relative Risk	95% CI
Stage III Disease and	Hyperfractionation Radiotherapy	16 (53%)	14 (47%)	0.07	1.7	0.93651 to 3.3748
Stage IV Disease	Conventional Radiotherapy	9 (30%)	21 (70%)			

Table 1. Stage and Complete Response Univariate Analysis

Variable	Category	Complete Response Present n (%)	Complete Response Absent n (%)	P Value	Relative Risk	95% C.I
Oral Cavity	Hyperfractionation Radiotherapy	8 (47%)	9 (53%)	0.690	1.176	0.529 to2.615
	Conventional Radiotherapy	6 (40%)	9 (60%)			
Oropharynx	Hyperfractionation Radiotherapy	3 (43%)	4 (57%)	0.193	3.857	0.503 to 29.55
	Conventional Radiotherapy	1 (11%)	8 (89%)			
Hypopharynx	Hyperfractionation Radiotherapy	4 (80%)	1 (20%)	0.157	2.400	0.713 to 8.076
	Conventional Radiotherapy	2 (33%)	4 (67%)			

Table 2. Site and Complete Response- Univariate Analysis (Subgroup Analysis)

Sl. No.	Reactions	No. of Patients	
		HF Group	CF Group
1.	Patchy Mucositis (Gr II)	14 (47%)	8 (27%)
2.	Confluent Mucositis (Gr III)	5 (17%)	2 (7%)
3.	Skin Reaction (Gr I)	16 (53%)	8 (27%)
4.	Skin Reaction (Gr III)	3 (10%)	-
5.	Xerostomia	13 (43%)	6 (20%)
6.	Odynophagia	3 (10%)	2 (7%)
7.	Hoarseness of Voice	1 (3%)	-

Table 3. Summary of Toxicities

DISCUSSION

Advanced Head and Neck cancers in Stage III and Stage IV presentation has a dismal prognosis and has to be effectively managed by aggressive treatment with combined modality or by altered fractionation schemes. Prolongation of the treatment duration is considered to be one of the causes of treatment failure in radiotherapy.[9] Regarding radiation dose fractionation has evolved from once daily dose to hyperfractionation and altered fractionation.[10][11] A split course regimen was compared to the uninterrupted radiation therapy in laryngeal cancers.[12] The tumour proliferation in this was compensated by administration of higher doses. Cell kinetic studies have shown that squamous cells of the head and neck tumours have very short T_{pot} of only 5 days or less.[13] These are the reasons for the development of short term protocols.[14] By using more than one fraction per day, it is possible to reduce the potential higher toxicity than when single high doses are given. The interfraction should be one enough to allow repair of normal cell and it is believed that 6h interfraction interval should be appropriate, hence in this present study too the same was followed.[14]

With hyperfractionation, a larger number of smaller than conventional fractions is given daily. The total dose is usually 10 - 15 percent greater than with standard fractionation and the total period of time is unchanged. The aim of

hyperfractionation is to achieve the same incidence of late effects on normal tissue as observed with a comparable conventional regimen, while increasing the probability of tumour control.

Historically, hyperfractionation was introduced to exploit the self-sensitising effect of cell-cycle redistribution present in tumour, but absent in late responding normal tissues. Hyperfractionation increases the therapeutic differential between late responding normal tissues and acutely responding tumours exploiting differences in their alpha/beta ratio. The third rationale for hyperfractionation is that the OER (Oxygen Enhancement Ratio) is low at lower doses.[15]

For comparison, the dose per fraction necessary for an isoeffect in acutely responding normal tissues and most tumour would be between 1.0 and 1.2 Gray.[14] Therefore, if two fractions of 1.2 Gy per day replaced one fraction of 2 Gy per day, the acute response of normal tissues and cytotoxicity for tumours would be increased as if the dose has been increased by 14%. Hyperfractionation has improved tumour control rates, but also increases acute toxicity.[16]

In the study involving 30 patients in hyperfractionation group, 14 and 16 patients were presented with stage III and IV disease respectively. The study was to assess the efficacy of hyperfractionation in locoregional tumour control. The total tumour dose used was 72 Grays with 1.2 Gy per fraction and treated with 2 fractions per day with interfraction interval of 6 hours to a total of 60 fractions in 6 weeks.

Since two fractions of 1.2 Gy per day replaced one fraction of 2 Gy per day, the acute response of normal tissues is increased by 14% as the overall treatment time is unchanged. So hyperfractionation resulted in an increase in acute toxicity as evident in the study.

Limitation of the Study

Sample size was small and was chosen as per convenience and the patient's input. Long term followup of the patients was not done.

CONCLUSION

Advanced Head and Neck cancers in stage III and IV presentation is an adverse prognostic factor and has to be managed vigorously. Various altered fractionation schedules conducted in such patients indicate that hyperfractionation in advanced head and neck cancers improves locoregional control rates by an approximate 15% without an overall increase in acute and late reactions. Hyperfractionation inevitably results in more severe acute reactions than in conventional fractionation. With the use of small dose fractions, hyperfractionation allows higher total dose to be administered and this translates into a higher biologically effective dose to the tumour than with conventional fractionation. Thus, in this present study we conclude that though loco-regional control was higher with hyperfractionation than conventional therapy, the acute toxicities were also more with hyperfractionation.

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