ORIGINAL ARTICLE

CONTINIOUS HYPERFRACTIONATED ACCLERATED RADIATION THERAPY IN HEAD AND NECK CANCERS - A PILOT STUDY

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ABSTRACT

Objectives: To assess the acute radiation reactions and immediate locoregional response of accelerated hyperfractionation radiotherapy in head and neck cancers.

Methods: A prospective study of 20 patients with squamous cell carcinoma of oropharynx, hypopharynx and nasopharynx with stage II – IV received continuous accelerated hyperfractionated radiotherapy (CHART) to a total dose of 54 Gy/36 fractions, dose per fraction of 1.5GY/fraction, 3 fractions /day given at 4-6 hours interval, 6 days / week with overall treatment time of 12 days.

Results: Patients were assessed as per UICC guidelines. 6 patients developed Grade 6 mucositis, 10 patients developed Gr 5 mucositis and remaining 4 patients developed only Gr 3-4 mucositis. All cases of Grade 5 and 6 mucositis resolved in 4 weeks. Majority of patients developed only erythema and patchy dry desquamation of the skin. 12 patients (60%) achieved complete response and 7 patients (35%) achieved partial response at 4-6 weeks after completion of therapy. Median follow up was 8 months.

Conclusion: CHART achieves good locoregional response in stages III and IV of head and neck cancer. The acute mucosal reactions were within acceptable limits. The compliance to the treatment was good.

Keywords: CHART, accelerated hyperfractionation, acute toxicities, head and neck cancers

INTRODUCTION

The Incidence of Head and Neck Cancers reported at our Institute is22.7% of all malignancies. Cancers arising from oropharynx and hypopharynx constitutes about 6.8% [1]. Majority of these patients present in advanced stage and definitive radiotherapy in terms of altered fractionation is a reasonable option for those medically unfit and/or refuse chemotherapy. This study offers a useful data for clinical practice and support of the radiobiological principle, cell kinetic studies of human tumors have suggested that volume doubling time commonly range from 30-120 days. Whereas in squamous cell carcinoma the mean potential doubling time of clonogenic tumor cells have been shown to be less than 5 days. This discrepancy is caused by cell loss which may be up to 90% in some tumors. When a course of radiotherapy is given the cell loss may be reduced leading to repopulation of a tumor while on treatment. This data has stimulated the study of accelerated schemes of fractionated radiotherapy[2,3,12].

To achieve tolerance of accelerated fractionation, an important factor is the number of fractions that can be given in the reduced number of treatment days. Radiobiological data have shown that radiotherapy given in multiple fractions reduces the severity of late morbidity however, it is also important that the repair of sublethal injury to be as complete as possible between fractions else normal tissue morbidity will be increased.

A scheme of radiotherapy "CHART" has been devised which gives continuous hyperfractionated accelerated radiotherapy with no gaps even over the weekend.

METHODS

This pilot study was conducted in the Department of Radiotherapy at Kidwai Memorial Institute of Oncology, Bangalore. Twenty patients with histologically proven squamous cell carcinoma grade III and IV of oropharynx, hypopharynx and nasopharynx stages II, III and IV with a KPS of 70 or more were included in this study.

The patients who had prior treatment with surgery/radiotherapy and/or chemotherapy, with history of diabetes, hypertension, tuberculosis or HIV were

excluded from the study. All patients underwent a thorough clinical examination, including indirect laryngoscopy, direct laryngoscopy and nasopharyngoscopy, complete hematology, radiography and cytopathology examination of the primary tumour or metastatic node was carried out.

All patients were hospitalized during therapy and necessary supportive treatment was given before radiotherapy. Pre radiotherapy dental evaluation was done in all patients. The written consent was obtained for all patients prior to therapy. The study was conducted as per ICH GCP guidelines & scientific committee approval. The patient characteristics are as shown in Table No.1.

Table 1: Patient Characteristics

Patient Characteristics		Patients (n=20)
Gender	Male	16
	Female	4
Age (yrs)	Range	30-75
	Median	53
KPS*	70%	9
	80%	8
	90%	3
Tumor site	Oropharynx	12 (60%)
	Hypopharynx	7 (35%)
	Nasopharynx	1 (5%)
Histology Grade	Gr III	17 (85%)
	Gr IV	3 (15%)
Stage**	II	1 (5%)
	III	9 (45%)
	IV	10 (50%)

*Karnofsky performance scale, **UICC staging 1987[4]

Radiotherapy: The initial treatment volume included gross disease in the primary and nodes with clearance and possible subclinical disease. The dose delivered to this volume was 45 Gy in 30 fractions, 3fractions/day, at an interval of 4-6 hours, at a rate of 1.5 Gy/Fr – 6 days a week. After a dose of 37.5 Gy spinal cord shielding was done. Following this, an additional 9Gy is given in 6 fractions, 3fractions/day, 1.5Gy/Fr to the gross disease in the primary and or nodes with 1-2 cm margin as boost. The total dose delivered to the locoregional disease is 54Gy/36F: 3F/day: 6 days/week over 12 consecutive days.

Technique: Depending on site and extent of lesion, eight patients were treated primarily by a two parallel opposing lateral fields which included primary disease and the entire group of cervical nodes. In twelve patients primary and upper neck was planned by two lateral parallel opposing fields and lower neck was planned by a single direct anterior field. Dose was prescribed at midplane for parallel opposing fields and at 3cms depth for anterior neck fields. In all patients planning was done under simulation, Boost therapy for gross loco-regional disease was delivered with reduced two parallel opposing lateral fields.

All patients were treated with megavoltage photons of energy 1.25 MV (Cobalt 60) at 80 cms SSD and electrons 9-12 Mev was used for posterior neck nodes overlying the spinal cord. Every set up was supervised by the radiation oncologists before execution of treatment.

Statistical analysis was done using R software (free download version). Descriptive statistics were generated for clinical parameters and association between two parameters was using non – parametric X^2 test or Fischer's Exact test wherever applicable. Any P values less than or equal to 0.05 was considered to be statistically significant.

RESULTS

There were twenty patients enrolled in this study of which sixteen were males and four were females, with the performance status of 70% to 90%. One patient was lost for follow up after the completion of the scheduled treatment hence the response was evaluated only in 19 patients with follow up period ranging from 4 months to 15 months, median of 8 months.

Eighteen patients had an uninterrupted course of radiation which was completed in an overall period of 2 weeks. Two patients had an interruption of one day during treatment. All patients were examined once weekly during the treatment, at the completion of treatment, and at monthly intervals during the first six months after completion.

Majority of patients developed mucositis of varied degrees (Table No.2) and symptomatic and supportive treatment were given with oral anti inflammatory drugs and steroids. All patients were hospitalized for varying periods of 12 days to 40 days. Five patients required Ryle's tube intubation and three patients required intravenous fluids for adequate nutrition. Hydration, protein/calorie intake and oral hygiene were adequately maintained for all patients during treatment.. Most of them developed severe mucositis by 10th to 12th day of treatment which reached the peak by third week and gradually healed by 4-5 weeks after treatment.

Table 2: Mucositis in study subjects

Grade	No. of patients
III	3
IV	1
V	10
VI	6

There was no correlation between mucosal reactions and radiation technique, because treatment with three field technique, and sparing the laryngeal or pharyngeal mucosa did not significantly reduce the reactions, and increase or alter the tolerance to treatment.

All cases of severe mucositis (Gr.6) were observed in patients where large volume of buccal mucosa and

oropharynx was irradiated.16 patients (80%) developed erythema and patchy dry desquamation (Grade III and IV) by third and fourth week of treatment. Four patients developed only erythema without any desquamation. There were no fatal complications observed during the study. The patients were assessed according to the UICC (WHO) criteria[5].

Patient's response to treatment was assessed as per UICC criteria[6]. The association between stage and response (P value = 0.60) and also the grade and response (P value = 0.98) did not show any statistical significance. Twelve patients (60%) achieved complete response at 4-6 weeks after completion of therapy at both primary and nodal sites, while 7 patients (35%) achieved partial response at primary and nodal sites(Table No.3). Grade III mucositis and grade -II skin reaction was observed during the treatment in the patient lost for follow up. Among 12 complete responders, with mean follow-up of 8 months, only 5 complained of dryness of mouth. The duration of response observed as complete and partial response is mentioned in Table No. 4.

Table 3: Stage Vs Response

Stage	CR	PR	Total
II	1	-	1
III	6	2	8
IV	5	5	10
Total	12 (60%)	7 (35%)	19

Table 4: Response Vs Duration

Follow up in months	6-9	9-12	>12
Complete Response	7	2	3
Partial Response	2	-	5

DISCUSSION

The clinical and radiobiological data suggests that both hyperfractionation and accelerated fractionation offer the prospect of improved therapeutic ratio. With two rational approaches to follow, one needs to know the relative effects on tumour control of reducing the dose per fraction versus reducing the overall time of treatment. The first depends on the Alpha to Beta ratio of clonogenic tumour cells, whereas the second depends on their regenerative capability (function of potential doubling time and cell loss factor of the tumour during therapy).

The continuous hyperfractionated accelerated radiotherapy (CHART) regimen can be compared with other designed fractionation regimes to overcome the problem of cellular repopulation by accelerating radiotherapy. Withers et al, in an analysis of clinical data derived from various studies concluded that cellular repopulation began 3-4 weeks after the initiation of treatment. Reduction of the overall treatment time by increasing the size of dose per fraction is also counter-productive, in that the probability of late normal tissue injury and mucosal toxicity is increased[7].

A regimen used in a clinical trial by the EORTC attempted to overcome this problem of early severe mucosal reactions by using a split course technique. In advanced head and neck cancer, a rest period of 3-4 week in the treatment could well have allowed the tumour, as well as normal tissues to repopulate. There was no difference in local tumour control or survival[8].

Wang, et. al, had also used a split course technique. A tumour dose of 64Gy was given over 6 weeks in 1.6 Gy fractions. 2frs/day with a 2 week rest period after the 12th day. Compared with previously treated patients, an improvement in local tumour control in head and neck tumours have been reported[9].Olmi, et .al reporting 161 patients with head and neck cancer who received 48-52 Gy in 2 Gy/fr, 3 fractions per day, over 11-12 days, gave an actuarial 5 year risk of late damage of 24%[10].

Percchia and Salti gave 48-54Gy in 2Gy/fr, 3 times a day, with 4 hour interfraction interval, although initial tumour regression was satisfactory, radionecrosis occurred in 55% and 2 year survival was only 14%[11].Lamb,et.al, have reduced the dose / fraction to 1.8 Gy and completed radiotherapy dose of 59.4 Gy in 24 days. The acute morbidity was considerable, 31% patients required total parenteral nutrition and reported 3 year locoregional control rate of 47%[12].

Marcial reported on a large series of patients with Head and Neck tumours in which a complete response was achieved in 66% of patients with T3, T4 N0 disease and the response with N3 disease dropped to 35%[13].Dische and Saunders, reported on 92 patients treated with continuous hyperfractionated accelerated radiotherapy using 1.5Gy/fr, 3frs/day with interfraction interval. of 4-6 hours to total doses of 54Gy over 12 days. CHART patients achieved a local tumour control of 90% falling to 49% by 36 months. T3, T4, No - N3 show tumour free rate 62% at 1 year. Ten patients required nasogastric feeding due to mucositis. Skin reactions were milder than with conventional therapy[14].

In our study, we achieved a complete response rate of 60% at median follow up period of 8 months. With an acceptable mucosal toxicity 5 out of 20 patients required nasogastric tube feeding. Skin reactions were minimal and late reactions encountered appear to be less pronounced. Tumor responses are comparable to conventional fractionation.

Since patients included in this study were hospitalized, the number of visits to the hospital for treatment was reduced and the duration of hospitalization in the majority of the patients was less than 4 weeks. This radiotherapy protocol has proved to be more economical. Especially in a Regional Cancer Centre, where patients come from distant places for daily treatment, this form of compressed radiotherapy seems to be beneficial and practical.

CONCLUSION

Through this study we conclude that CHART achieves good locoregional response in stages III and IV of head and neck cancer. The acute mucosal reactions were within acceptable limits. The compliance to the treatment was good. However further trials with long term follow up are required to study the late effects and survival.

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