

Evaluation of fractionation in the form of six fractions per week radiotherapy schedules in locally advanced head and neck cancers

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Citation

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Abstract

Aims and objectives To evaluate the feasibility and efficacy of six fractions per week radiation schedules in terms of loco-regional control of the tumor and radiation induced side effects in locally advanced head and neck cancer patients.

Materials and methods One hundred and twenty seven previously untreated, histopathologically confirmed, stage III and stage IV, locally advanced squamous cell carcinoma of head and neck patients were included in the study. All the patients were given radical radiotherapy. The patients were given a dose of 66 Gy over 33 fractions in 5.3 weeks. All the patients were evaluated in terms of treatment response, treatment related toxicity and survival.

Results

One hundred and twenty seven patients were available for final evaluation. Median age of presentation of patients was 55 years. 48% of patients had stage III disease. Skin and mucosal toxicity were most common side effect observed during treatment. Complete response observed in 77% of our patients while 21% showed partial response. **Conclusion** Six fractions per week radiation schedule had shown superior tumor control, but at the same time produced higher but acceptable mucosal toxicity. In view of the encouraging local control and acceptable radiation toxicity this trial continues to enroll more patients. Supportive care can be used effectively to overcome the toxicities associated with this treatment.

INTRODUCTION

Head and neck cancers are the commonest neoplasm seen in India accounting for significant morbidity and mortality. Every year about 700,000 to 900,000 new cases are detected in India, accounting for one fourth of male and one tenth of female cancers.^{1,2} Approximately 70%-80% are diagnosed with locally advanced disease with lymph node involvement in up to 30%-50% of cases.^{3,4} Because of high incidence of advanced disease at presentation and local failure rates of 50%-60% the management of head and neck carcinomas is a challenging proposition.⁵

Over the past few years oncology has rapidly advanced in various fields especially surgery, radiotherapy and chemotherapy. However, for local cure, surgery and radiotherapy are two standard curative modalities available for squamous cell carcinoma of head and neck.^{6,7} Local cure rate for stage I and II are 80%-90% and 50%-70% respectively.^{4,7} For a given early lesion, radiotherapy is

generally chosen as the primary form of management but for locally advanced tumors, treatment with surgery and radiotherapy or both is associated with poor long term survival because of the local failure (60%) and development of distant metastasis (10%).⁸

Hence, radiotherapy remains the mainstay of treatment in locally advanced cases and in early stages if organ preservation is required.^{4,7}

Conventional radiotherapy has been shown to produce favorable results in early carcinomas of head and neck (T1 & T2 tumors) with cure rates of 80%-90% and 50%-70% respectively. For the locally advanced carcinomas (T3 & T4 tumors) the loco regional control rate is extremely poor with 3 year disease free survival of about 25%-30%.⁹

So, various strategies to modify the radiation response have been tried like hyperbaric oxygen,¹⁰ hyperthermia,¹¹ low LET radiations,¹² high LET radiations,¹³ but to date these

strategies have failed in demonstrating a clinically significant advantage.

Thus, came the concept of altered fractionation schedule for improving treatment outcome. According to Withers HR and colleagues, it has been well documented that prolonged treatment time may reduce the chance of tumor control and reduction in overall treatment time may result in improved tumor control.¹⁴ Various modification in fractionation schedules have been done like hypofractionation, hyperfractionation, accelerated fractionation to enhance the locoregional control of the disease in locally advanced cases of head and neck cancer.

Delivering a high dose with conventional fractionation schedule that needed for adequate tumor control is practically very difficult due to acute dose limiting reactions. Therefore, any treatment modality which would shorten the treatment time and thereby advantageous from radiotherapeutic point of view and from economical point of view and require no extra resources seems to be suitable for patients, especially for centers with limited resources such as those in India and in many other developing countries.

MATERIALS AND METHODS

One hundred twenty seven patients of locally advanced squamous cell carcinoma head and neck region were studied from September 2006 to December 2008 in this prospective trial. Only the patient where external radical radiotherapy was the primary line of management was included for this study. After complete history taking and complete physical examination the patients underwent base line investigations including complete blood count, kidney function and liver function tests. Chest X ray and X ray soft tissue neck lateral view and X-ray PNS etc depending on the site of primary tumor. Investigations such as barium swallow, ultrasound abdomen and CT scan were done if required to rule out distant metastasis or to assess the extent of the disease. After examination and investigations all patients were staged according to International TNM classification of UICC(1998).The exclusion criteria included previously treated patients with surgery, radiotherapy or chemotherapy, tumor classified as stage I &II, distant metastasis , existence of multiple malignancies, patients with Karnofsky performance status < 70, participation in any other related clinical study during the past\ present and patient having some associated medical condition making them unsuitable for radical treatment. The patients received external beam irradiation on Cobalt 60 Teletherapy machine. All patients

were planned with proper field placement and verification was done utilizing Simulator with Digital Therapy Imagined (DTI) facility. All the patients were treated using parallel opposed technique covering the primary tumor with its local extensions, the regional lymphatic drainage areas and tailored according to the need of individual patient. The shrinking field technique was used and the spinal cord was excluded from the radiation field after a dose of 44 Gy. One hundred twenty seven were planned to receive a total radiation dose of 66 Gy in 33 fractions over 5.3 weeks period with dose of 200 cGy per fraction dose in six days a week schedule. During the treatment period all patients were examined weekly for radiation reactions over the skin , oral mucosa in accordance with the 9 levels of WHO radiation toxicity scoring. Similarly patients were evaluated for gastrointestinal toxicity like nausea, vomiting and hematological toxicity according to the WHO's grade scoring criteria. After the completion of treatment all the 127patients were followed up , first fortnightly for one month then every month for a year, two monthly in second year and three monthly in third year . Patients were evaluated for radiation reactions, and effects of treatment on the primary tumor site and regional metastasis were assessed. The usual statistical methods had been utilized to assess, analyze, compare and evaluate the so obtained observations and data for both the groups.

RESULTS

The median age of presentation of patients in the study was 55 years. There were 118(92.91%) male and 9(7.08%) female patients. Commonest site of presentation was Oropharynx. 48% of patients had stage III cancer. Among the patients all the male patients were smokers, with a mean duration of smoking of 20 years. Dysphagia and pain were the most common presenting symptoms in 47% of patients. All the patients completed scheduled dose of radiation therapy and were available for evaluation. (Table 1)

Figure 1

Table.1. Patients Characteristics

Characteristics	No. of patients(n=127)	%
Age		
30-40	8	6.2
41-50	33	25.98
51-60	45	35.43
61-70	37	29.13
71-80	4	3.14
Median	55	
Sex		
Male	118	92.91
Female	9	7.08
Socioeconomic Status		
Rural Status	90	70.86
Urban Status	37	29.13
Personal Habits		
Smokers	110	86.61
Non-Smokers	17	13.38
Presenting symptoms		
Dysphasia & Pain	60	47.24
Hoarseness of voice	18	14.17
Swelling neck	37	29.13
Ulcer	12	9.4
Primary site		
Oral cavity	13	10.23
Oropharynx	53	41.73
Hypopharynx	17	13.3
Larynx	44	34.64
Stage		
Stage III	61	48.03
Stage IV A	58	45.66
Stage IV B	8	6.2

The treatment response, the clinical status of the patients at the last follow up, the skin toxicities and the mucosal toxicities recorded and the survival curve are shown in the following tables (Tables 2,3,4,5) and the figure (Figure 1)

Figure 2

Table.2. Observed Combined loco-regional response at the end of radiotherapy

Parameter	No. of Patients	Response(%)
CR at both sides	98	77.16
PR at both sides	27	21.25
Objective response (CR+PR)	125	98.25
NR at both sides	2	1.5
PD at both sites	0	0

CR- Complete response
NR- No response

PR- Partial response
PD- Progression of disease

Figure 3

Table 3: Clinical status at the last follow up

S.No	Status	Number of patients (N=110)	%
1.	Disease free survival	76	59.85
2.	Stable disease	15	11.81
3.	Recurrence	09	7.08
4.	Death	10	7.87
5.	Lost to follow up	17	13.38

Figure 4

Table.4. Mucosal toxicity observed during treatment.

Toxicity Levels	1 st week n(%)	2 nd week n(%)	3 rd week n(%)	4 th week n(%)	5 th week n(%)	6 th week n(%)	7 th week n(%)
0	39(30.7)	0	0	0	0	0	0
1	21(16.5)	0	0	0	0	0	0
2	68(53.54)	85(67)	43(33.8)	21(16.5)	0	0	0
3	0	43(33.8)	84(66.4)	43(33.8)	21(16.5)	13(10.2)	0
4	0	0	0	46(36.2)	64(50)	68(53.54)	0
5	0	0	0	29(22.3)	43(33.8)	46(36.2)	0
6-9	0	0	0	0	0	0	0

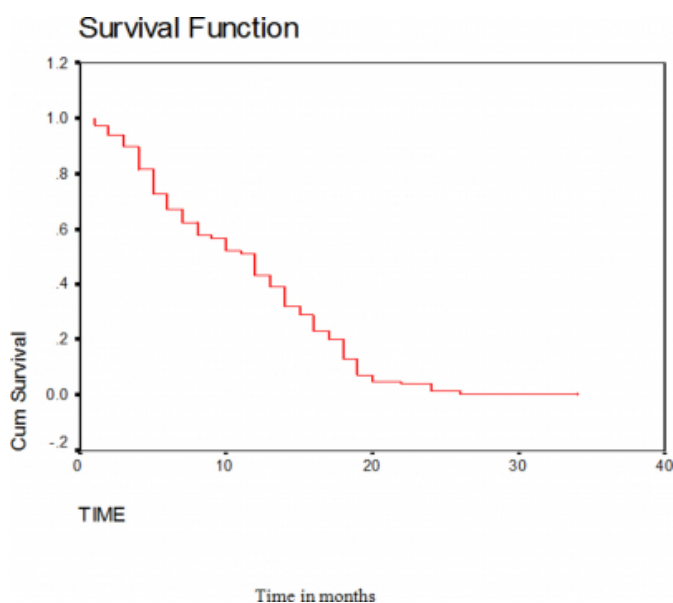
Figure 5

Table.5. Skin toxicity observed during treatment.

Toxicity Levels	1 st week n(%)	2 nd week n(%)	3 rd week n(%)	4 th week n(%)	5 th week n(%)	6 th week n(%)	7 th week n(%)
0	55(43)	55(43)	29(22.8)	0	0	0	0
1	72(57)	0	0	0	0	0	0
2	0	72(57)	81(63.7)	46(36.2)	0	0	0
3	0	0	17(13.3)	59(46.45)	59(46.45)	39(30.7)	0
4	0	0	0	21(16.5)	55(43.3)	68(53.5)	0
5	0	0	0	0	13(10.2)	21(16.53)	0
6-9	0	0	0	0	0	0	0

Figure 6

Figure1. Survival curve was generated by the Kaplan-Meier method and compared with long rank test. The median follow up time from the date of registration was 35 months. Statistical analysis was performed using SPSS software 10 (Statistical Package of Social Science, Chicago, IL).



DISCUSSION

Among the newly diagnosed malignancies of head and neck nearly 60% presents with locally advanced disease.¹⁵ Despite all strategies locoregional failure is common as a results of recurrence. Radiotherapy has been the most common nonsurgical treatment modality for locally advanced disease of head and neck carcinomas.¹⁵ Current clinical research efforts are directed towards decreasing local failure. It is hoped that it will, translate into an improvement in long term survival.¹⁶ Radiotherapy has been used with various fractionation schedules in order to improve the local control rate, with minimal radiation morbidity viz, conventional fractionation, hyperfractionation schedule or accelerated hyperfractionation schedules.¹⁷ The first altered fractionation schedule tried was hyperfractionation. It is defined as using multiple fractions of smaller size per day over the same treatment time to achieve an increase in the total dose.¹⁸

Since the fractions are repeated at shorter intervals in hyperfractionation, it may result in incomplete repair of sublethal damage thus decreasing the therapeutic ration.

In pure accelerated fractionations, the overall treatment time is reduced without concurrent changes in the fraction size of total dose which can be achieved if weekly number of fractions be increased without increasing the dose per fraction.¹⁹

Rationale for accelerated fractionation is a reduction of overall treatment time, thereby decreasing the opportunity for tumor cell to regenerate during treatment and therefore increasing the probability of tumor control for a given total dose.²⁰ During that time, the tumor overtly shrinks and regresses; the survival clonogenes divide and increase in number more rapidly than ever. Hence, particularly in head and neck carcinoma, radiotherapy should be completed as soon as after it has begun.

A therapeutic gain should be realized, provided the size of dose per fraction is not increased and the interval between dose fraction is sufficient for complete repair to take place.

The present study was conducted to evaluate the six fractions per week radiotherapy schedules in locally advanced head and neck carcinoma patients. The study was meant to evaluate the feasibility and efficacy if any of six fractions per week (pure accelerated hyperfractionation) radiation schedules in terms of locoregional control of the tumor and radiation induced effects. All the patients were

followed upto 30 months after completion of treatment. Complete response (according to WHO criteria) was 77% at the end of first month of follow up. Partial response was 21%. Overall response (CR+PR) observed in 98.42% of patients. After completion of last follow up 76 patients (59.85%) had disease free survival, 15 patients (11.51%) had stable disease, 9 patients (7%) developed recurrence disease at primary site.

Overgaard et al conducted a comparative study in squamous cell carcinoma head and neck, by giving 66 Gy either 5 or 6 fractions per week. After a follow up time of 5 years locoregional control rate was 66% for the patient who underwent 6 fractions per week compared with 57% for patients who underwent 5 fractions per week schedule. The benefit in tumor control resulted in a significant better overall disease specific survival (65% vs. 72%) for 5 vs 6 fractions per week.²¹

Hliniak et al did a multicentre trial by two fraction regime compared with conventional regime in 395 patients with laryngeal cancer patients. Conventional arm received 66Gy in 33 fractions over 45 days. Accelerated fractionation arm received 66Gy in 33 fractions over 38days. AF showed better locoregional control and better prognosis compared with conventional arm.²² As compared with control group and other reference studies, the result of present study showed significant difference in the outcome of the response.

The various acute reaction effects on the skin as per WHO Level observed during treatment. During the first week, 56 patients showed threshold erythema (WHO Level 1) which settled by 4th or 5th days of the treatment. Definite erythema (WHO Level 2) was noticed in 56% versus 46% patients.

During the third week 63% patients developed definite erythema while 13.3% patients developed erythema with desquamation.

Dry desquamation (WHO Level 4) was observed in 16.6% patients, during the 4th week of the treatment. During the 5th week desquamation with blistering (who level 5) was observed in 10% of patients. During sixth week Level 4 reaction were noted in 5.3% of patients, while level 3 were observed in 30% patients. Level 5 reactions were observed in 16.6. No patient developed level 6 or higher level of reactions. Although the patients developed skin reactions more rapidly and in large number, however, they were manageable.

Mucosal reaction observed in 16.6% of patients during the first week. At the end of first week 53.3% of the patients developed definite erythema (WHO Level 2). During the 2nd week of treatment, more number of patients had definite erythema while 33.3% patients developed patchy mucositis in less than half of the field. During the 3rd week, definite erythema and patchy mucositis was seen in 33.3 % patients.

During the 4th week 11 patients developed patchy mucositis in more than half of the field (WHO Level 4) and 7 patients (23.3%) also developed confluent mucositis. At the end of 5th week of treatment patients had level 5 mucosal reactions. At the end of treatment 36.6% patients had confluent mucositis. However, all the patients in the study group were able to complete the radiation treatment during the planned period. Most of the reported literature on accelerated fractionation showed higher grades of mucositis as compared to conventional fractionation.

A study conducted by Overgaard et al over 1,476 patients using six fractions per week versus five fractions per week radiation schedule in all stages (I-IV) head and neck squamous cell carcinomas has shown that about 53% of patients in accelerated arm developed mucositis compared with 33% in the conventional arm mucositis persisted longer in the accelerated arms and all patients took about 3 months for healing from the onset of treatment. Similar findings have been observed in present study.²³

Lee et al conducted a study on treating nasopharyngeal carcinoma with accelerated fractionation comparing with conventional fractionation over 325 patients. Patients who were treated with accelerated fractionation showed significantly higher incidence of acute reaction grade > 3 (72% versus 13%) as against conventional arm. But no patient developed grade 4 or 5 toxicity and all the patients were able to complete the radiation treatment. 36.6% patients in the study group and 23% patients in control group received supportive treatment in the form of parenteral nutrition and intravenous fluids as oral intake in these patients decreased due to severe mucositis.²⁴ However, all the patients in both the group were able to complete the schedule in the planned treatment. The completion of the planned treatment required parenteral nutrition and hospitalization in 34% to 87% of patients as reported by Maciejewski et al and Hariot et al.^{19, 25}

Maciejewski et al evaluated a randomized clinical trial on 44 patients with head and neck squamous cell carcinoma in

stage T2-4N 0-1M. They used total dose of 70Gy in 35 fractions at an interval of 24 hours (dose per fraction being 2 Gy) on all week days (dose per week being 14Gy) over 5 weeks. Conventional arm received the same total dose in same number of fractions but over 7 weeks. Treatment was accelerated by 2 weeks. Analysis of the severe mucosal reactions showed significant difference in regard to the severity and duration of mucositis. Mucosal reactions were observed one week after starting the treatment, its severity increased between days 14-21 to reach confluent mucositis covering the entire field in 48% of patients as compared to the 5% in the conventional arm, and lasted longer than three weeks. Supportive treatment was given in 87% of study group patients versus in 46% of the patients in conventional arm. 30% of patients in study arm developed osteonecrosis and soft tissue necrosis during the 7-12 months follow up versus in 10% of patients in conventional arm. Persistent edema of epiglottis was observed during the 6-13 weeks after the completion of treatment in 26% of the patients. There was a significant association between acute reactions and late effects in the study group suggesting that the late effects are consequential. Early tumor regression was seen in 83% of the study group patients versus 62% in control group patients. Complete nodal regression was seen in 100% versus 73% in study versus control group. Although there was an improvement in the early tumor response obtained within 7 days regime the high incidence of severe acute reactions and consequential late effects (30%) gave unacceptable toxicity. Also in this trial patients with N2 N3 disease were not included and hence this regime was not encouraged. Because of these reasons this schedule was modified using small dose per fraction i.e. 1.8 cGy in both the arms and 3 day break was given every weekend in the study arm. In the modified schedule 3 years locoregional control was 82% vs 37% with overall survival 78% vs 32 % (AF/CF). Severe mucositis was seen in 62% vs 26% with late complications 10% vs 0%.²⁶

Jackson SM et al conducted a trial at Vancouver Cancer Center in neck and head cancer patients of 10 fractions per week (dose per fraction 2Gy) in which they shortened the overall treatment time from 45-48 days to 22-25 days. They delivered a total dose of 66Gy. A significantly greater proportion of grade 4 late reactions occurred in the accelerated fractionation group than in the control group leading to the premature termination of the study.²⁷

CONCLUSION

In terms of clinical response at completion of treatment and follow ups the results of our study are well comparable with other references and with the control group the results are better. Accelerated hyperfractionation in the form of 6 fractions per week showed a better response and found to be well tolerated at all the follow ups and showed encouraging response in terms of complete and partial response. However, the main constraint of this regime is skin and mucosal reactions during treatment.

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