

Prospective randomized trial to compare the outcome and tolerability of delivering the same total dose of radiation in 6 1/2 weeks versus 5 1/2 weeks time in head and neck cancers

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Abstract

Background: Concurrent chemoradiation is currently considered to be the standard of care in the treatment of head and neck cancer. In developing countries like ours, a good number of patients cannot tolerate chemoradiation because of the poor general condition and financial constraints. Those patients are treated with radiation alone. The optimum radiotherapy (RT) schedule for best local control and acceptable toxicity is not yet clear. We aimed to find out whether shortening of treatment time using six instead of five RT fractions per week improves the locoregional control in squamous cell carcinoma of head and neck. **Materials and Methods:** We conducted a prospective randomized study for a period of 2 years from September 2007 to August 2009 in 109 untreated patients of squamous cell carcinoma of head and neck with histologically confirmed diagnosis and no evidence of distant metastasis. Study group (55 patients) received accelerated RT with 6 fractions per week (66 Gy/33#/5 1/2 weeks). Control group (54 patients) received conventional RT with 5 fractions per week (66 Gy/33#/6 1/2 weeks). Tumor control, survival, acute and late toxicities were assessed. **Results:** At a median follow-up of 43 months, 29 patients (52.7%) in the 6 fractions group and 24 patients (44.4%) in the 5 fractions group were disease-free ($P = 0.852$). The benefit of shortening was higher for advanced disease control though it was not statistically significant. Grade 3 and 4 skin toxicity was significantly higher in the accelerated RT (70.9%) arm as compared to conventional (35.1%) arm ($P = 0.04$). Grade 3 mucositis was significantly higher in the accelerated RT arm (32.7% vs. 16.6%; $P = 0.041$). Those acute toxicities were managed conservatively. There was no difference in late toxicities between the two arms. **Conclusion:** Use of 6 fractions per week instead of 5 fractions per week is feasible, tolerable, and results in a better outcome in the patients of head and neck cancers.

Key words: Accelerated fractionation, head and neck cancer, radiotherapy

Introduction

Squamous cell carcinoma of the head and neck is predominantly a locoregional disease and the primary treatment methods are surgery and radiotherapy (RT), with RT being the favored treatment if organ preservation is required.^[1] The optimum RT schedule for best local control and acceptable toxicity is not yet clear. When treating squamous cell carcinoma of head and neck by RT, there is a need to optimize the irradiated volume, total dose, dose/fraction, and overall treatment time. Whether the conventional system of fractionation (i.e., 60–70 Gy in 2 Gy fractions, 5 times a week) is the optimal way of delivering RT in all circumstances is highly debatable. One of the most important biological factors related to the outcome of RT in squamous cell carcinoma of the head and neck is the proliferation of tumor stem cells during treatment. A cause of resistance with conventional fractionation RT could be radiation-induced accelerated proliferation of clonogenic tumor cells. A reduction in the chance of tumor control through the lengthening of treatment times has been clinically and biologically documented.^[2] Furthermore, in a substantial number of clinical reports, reduction in the total treatment time has improved tumor control.^[3–5] A shorter treatment time can be accomplished by applying a higher dose per fraction, but this change will disproportionately increase the rate of late complications. Accelerated treatment is therefore only possible if the weekly number of fractions is increased without increasing the dose per fraction. This shortening of overall treatment time should limit the extent of accelerated repopulation and therefore one may expect an increase in the probability of tumor control for given total dose.^[6] Since treatment time is thought to have little or no

influence on the response of late reacting normal tissue, a reduction in overall treatment time would not be expected to affect the incidence and severity of late normal tissue injury. At the same time, reducing overall treatment time will increase the turnover on machine, thus will reduce the waiting list also, especially in a busy department like ours with limited resources. Keeping above facts in mind, we have planned a randomized clinical trial to test the efficacy of shortening the overall treatment time from 6 1/2 weeks to 5 1/2 weeks by delivering six fractions per week instead of five fractions per week in the treatment of head and neck cancers in our institution with the aim to find out whether shortening of overall treatment time by use of this regimen is tolerable and improves the tumor response.

Materials and Methods

In our institution, we conducted a prospective randomized study for a period of 2 years from September 2007 to August 2009 in 109 untreated patients of squamous cell carcinoma of head and neck with histologically confirmed diagnosis and no evidence of distant metastasis.

Criteria for eligibility were age <75 years, Karnofsky Performance Status score >70, stage T₁–T₄, N₀–N₃, M₀, invasive squamous cell carcinoma of the larynx, oropharynx, and hypopharynx (oral cavity, nasopharynx not included); no previous treatment for the malignancy, normal hematological, renal and hepatic function status.

Pretreatment protocol

A complete history was recorded, and thorough physical examination including local examination of disease, neck examination, indirect laryngoscopy, direct laryngoscopy, cytology, and biopsy were done. Baseline investigations like complete

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blood count, blood biochemistry, urine routine and microscopic examination were also done. All patients underwent dental checkup before RT and in patients who had undergone dental procedure a minimum gap of 2 weeks was maintained between procedure and beginning of RT. Radiographic examination included X-rays chest and soft tissue neck. Contrast-enhanced tomography of head and neck was also done. The patients were staged as per AJCC staging manual 2002.

Randomization

Before randomization, we stratified patients according to sex, tumor site, and stage of the disease. With the stratified randomization technique, patients were randomized into two groups.

- Study group: (Arm-A): Received accelerated 6 fractions per week RT - 66 gray/5½ weeks/33# (Monday – Saturday; one fraction/day)
- Control group: (Arm-B): Received conventional 5 fractions per week RT 66 gray/6½ weeks/33# (Monday – Friday; one fraction/day).

Treatment details

Patients were treated with external beam RT given with Co-60 beams using bilateral parallel opposed fields and three fields. Thermoplastic cast was used for immobilization in all the patients. Initially, the radiation portals encompassed primary disease, involved lymphnodes and 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 44 Gy/22#, the posterior neck field was reduced to spare spinal cord. After the microscopic disease had received 50 Gy/25#, the field was reduced to include involved lymph node region with one level up. After 60 Gy, the field was reduced to include involved primary sites with primary echelon and involved lymphnodes.

Assessment

Assessment for toxicity was done at every week during treatment and at the end of treatment toxicity was assessed according to the Radiation Therapy Oncology Group toxicity criteria. The scores were based on the patient's subjective symptoms, objective examination findings and treatment of the symptoms. At the completion of treatment, toxicity status and loco-regional disease status of all patients were recorded. The response was considered to be complete if there was complete regression of disease with no visible or palpable disease, partial if there was more than 50% regression in the lesion in maximal diameter, stable if lesion regressed <50% in maximal diameter and progressive if lesion increased by 25% or appearance of new lesion or secondary metastatic disease.

Follow-up

The first follow-up was done at 6 weeks. The subsequent follow-up was 2 monthly for the 1st year, followed by 4 monthly for 2 years and 6 monthly thereafter. Side effects of treatment that occurred within 90 days of the start of RT were considered acute effects and those occurring or persisting more than 90 days after the start of RT were considered late effects. Patients who had a recurrence or persistent disease were considered for salvage surgery if feasible. Palliative chemotherapy was administered in patients in whom surgery was not feasible.

Results

Patient characteristics

Most of the patients in this study were males. The median age of presentation was 56 years ranging from 22 to 78 years. Larynx was the most common primary site (64.2%) followed by oropharynx (20.2%) and hypo pharynx (15.6%). Among all the subsites, supraglottis was the most common subsite (51.4%) involved. Base of tongue and pyriform fossa were the most common subsites among oropharynx and hypopharynx, respectively. Most of the patients were of the locally advanced stage with stage IV being the most common (55.04%). Patients were well-balanced between the two groups in terms of T and N stage as shown in Table 1.

Locoregional control and survival

At first follow-up, that is, after 6 weeks of completion of treatment, 50 patients (90.9%) had complete response (CR) of the local disease in the accelerated RT arm and in the conventional RT arm CR of local disease was seen in 44 patients (81.5%). At first follow-up, CR of nodal disease was 89.1% and 75.9% in the accelerated and conventional RT arm, respectively. At a median follow-up of 43 months, CR was seen in 29 patients (52.7%) in the accelerated RT arm and 24 patients (44.4%) in the conventional RT arm were able to achieve CR [Table 2]. At a median follow-up of 43 months, disease-free survival was 48% in the accelerated RT arm as compared to 39% in the conventional RT arm [Figure 1]. Though this difference was not statistically

Table 1: Patient characteristics

Patient characteristics	No (%)	
	Six fractions per week	Five fractions per week
Sex		
Male	51 (92.7)	45 (83.3)
Female	4 (7.3)	9 (16.7)
Primary site		
Larynx	37 (67.3)	33 (61.1)
Oropharynx	10 (18.2)	12 (22.2)
Hypopharynx	8 (14.5)	9 (16.7)
Subsites		
Glottis	8 (14.5)	6 (11.1)
Supraglottis	29 (52.7)	27 (50)
Tonsil	3 (5.5)	3 (5.6)
Base of tongue/vallecula	7 (12.7)	9 (16.7)
Pyriform fossa	6 (10.9)	8 (14.8)
Posterior pharyngeal wall	2 (3.6)	1 (1.9)
T stage		
T1	1 (1.8)	2 (3.7)
T2	27 (49.1)	19 (35.2)
T3	13 (23.6)	13 (24.1)
T4	14 (25.5)	20 (37)
N stage		
N0	15 (27.3)	12 (22.2)
N1	14 (25.5)	19 (35.2)
N2	25 (45.5)	20 (37)
N3	1 (1.8)	3 (5.6)
Composite stage		
I	0 (0)	2 (3.7)
II	7 (12.7)	7 (13)
III	17 (30.9)	16 (29.6)
IV	31 (56.4)	29 (53.7)

significant ($P = 0.09$), it showed a favorable impact of accelerated fractionation. There was no difference in overall survival between the two arms [Figure 2]. On subset analysis, the trend of better response with accelerated fractionation was seen preferably in the larynx and in advanced disease though it did not reach statistical significance. There was also a better trend in terms of locoregional control with accelerated fractionation among 50–65 years of age group as shown in Table 3.

Pattern of failure

When the pattern of failure was assessed by the site of the primary tumor and regional lymph nodes, nodal failure was similar in both the arms. Local failure was lesser in the accelerated RT arm as compared to conventional one though it was not statistically significant ($P = 0.89$). as shown in Table 4

Toxicities

Acute toxicity

Grade 3 and 4 skin toxicity was significantly higher in the accelerated RT (70.9%) arm as compared to conventional (35.1%) arm ($P = 0.04$). There was no difference in Grade 1 and 2 mucosal toxicity between the two arms. The majority of patients developed grade 2 mucositis (62.38%). However, Grade 3 mucositis was significantly higher in the accelerated RT arm (32.7% vs. 16.6%; $P = 0.041$) as shown in Table 5. Laryngeal toxicities ranging from G0 to G3 were seen in patients during treatment in both the arms but in the accelerated RT arm grade 2 and 3 laryngeal toxicities were significantly higher (85.4% vs. 35.1%; $P = 0.02$). The higher-grade pharyngeal toxicity (i.e., G2 and G3) was more commonly seen in patients of the accelerated RT arm and low-grade (i.e., G1) toxicity was commonly seen in patients of conventional RT arm. The frequency of G2 salivary gland toxicity was higher in the accelerated RT arm (58.1%) as compared to the conventional RT arm (18.5%). The difference was statistically significant ($P = 0.001$). Acute toxicities were significantly higher among patients between 50 and 65 years of age. There was also a greater percentage of Grade 3 acute toxicities in patients of more than 65 years, however, it was not statistically significant as shown in Table 6. The more frequent mucosal reactions in the accelerated treatment group resulted in a significantly increased use of tube feeding during accelerated treatment (20.4%) compared with the conventional treatment group (10.9%). Three-fourth of the patients older than 65 years required nasogastric tube feeding. None of our patients underwent feeding jejunostomy. Treatment was interrupted in 11% of patients in the accelerated RT arm and 6% patients in the conventional RT arm though it was not statistically significant.

In the majority of the patients, the skin reactions had healed on first follow-up (i.e., 6 weeks after completion of radiation

therapy). In conventional RT arm, the skin reactions were healed in all the patients whereas in accelerated RT arm, 10 patients (18.2%) were still healing with granulation tissue. On first follow-up, mucositis was completely healed in the majority of patients in both the arms. In the accelerated RT arm, mucositis had not completely healed in 9 patients (16.4%). Whereas in conventional RT arm, all the patients were with completed healed mucositis on the first follow-up.

Table 2: Type of response

Type of Response	6#/week (%)	5#/week (%)
CR	29 (52.7)	24 (44.4)
PR	15 (27.2)	17 (31.4)
SD	3 (5.4)	4 (7.4)
PD	8 (14.5)	9 (16.6)

Table 3: Subset analysis of locoregional control (CR)

	6#/week(%)	5#/week(%)	P
Sex			
Male	27 (52.9%)	20 (44.4%)	0.41
Female	2 (50%)	4 (44.4%)	0.87
Age (years)			
<50	5 (62.5%)	4 (57.1%)	0.85
50-65	22 (55%)	17 (40.4%)	0.19
>65	2 (33.3%)	3 (50%)	0.31
Site			
Larynx	22 (59.4%)	16 (48.4%)	0.37
Oropharynx	4 (40%)	5 (41.6%)	0.94
Hypopharynx	3 (37.5%)	3 (33.3%)	0.87
T stage			
T1-2	13 (46.4%)	9 (42.8%)	0.81
T3-4	16 (59.2%)	15 (45.4%)	0.30
N stage			
Node negative	6 (40%)	4 (33.3%)	0.74
Node positive	23 (57.5%)	20 (47.6%)	0.48

Table 4: Pattern of failure

Site of failure	6#/week (%)	5#/week (%)
Local	6 (10.9)	9 (16.6)
Nodal	7 (12.7)	7 (12.9)
Local+Nodal	5 (9.1)	7 (12.9)
Distant	7 (12.7)	5 (9.2)

Table 5: Acute toxicities

Acute toxicities	6#/week (%)	5#/week (%)
Skin toxicities		
Dry desquamation	16/55 (29.1)	31/54 (57.4)
Moist desquamation	33/55 (60)	15/54 (27.7)
Skin ulceration	6/55 (10.9)	4/54 (7.4)
Mucositis		
Patchy mucositis	31/55 (56.3)	37/54 (68.5)
Confluent mucositis	18/55 (32.7)	9/54 (16.6)
Laryngeal toxicities		
Grade 2	41/55 (74.5)	18/54 (33.3)
Grade 3	6 (10.9)	1/54 (1.8)
Pharyngeal toxicities		
Grade 2	31/55 (56.3)	20/54 (37)
Grade 3	21/55 (38.1)	11/54 (20.3)
Tube feeding	12/55 (21.8)	7/54 (12.96)
Salivary toxicity		
Grade 1	18/55 (32.7)	40/54 (74)
Grade 2	32/55 (58.1)	10/54 (18.5)

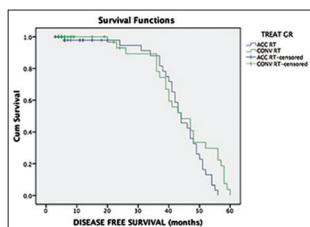


Figure 1: Comparison of disease-free survival between accelerated radiotherapy (RT) and conventional RT

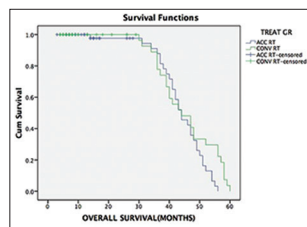


Figure 2: Comparison of overall survival between accelerated radiotherapy (RT) and conventional RT

Table 6: Toxicity profile according to age

	Age (years)	6#/week (%)	5#/week (%)	P
Grade 3-4 Skin reactions	<50	4 (50)	2 (28.5)	0.23
	50-65	31 (77.5)	14 (33.3)	0.00005
	>65	4 (66.6)	3 (50)	0.31
Grade 3 Mucositis	<50	3 (37.5)	2 (28.5)	0.75
	50-65	11 (27.5)	4 (9.5)	0.04
	>65	4 (66.6)	3 (50)	0.62
Grade 3 Dysphagia	<50	2 (25)	2 (28.5)	0.89
	50-65	16 (40)	5 (11.9)	0.004
	>65	5 (83.3)	4 (66.6)	0.59

On first follow-up, the majority of patients were having Grade 1 salivary gland toxicity. In the accelerated RT arm, 36 patients (65.5%) were having G1 and 16 patients (29.1%) were having G2 toxicity. In conventional RT arm, 50 patients (92.5%) were having G1 and 3 patients (5.6%) were having G2 salivary gland toxicity.

Late toxicities

We have observed late skin toxicities in the form of depigmentation, subcutaneous edema, and subcutaneous fibrosis. Subcutaneous fibrosis was present in 8 patients (14.5%) in the accelerated arm and 5 patients (9.3%) in conventional RT arm. This difference was statistically not significant ($P = 0.38$). There was no significant difference in late salivary toxicities between the accelerated and conventional RT arms.

Discussion

Accelerated RT improves locoregional control in squamous cell carcinoma of head and neck, shown in different prospective randomized studies.^[7] Accelerated regimens have been shown to increase treatment-associated acute morbidity, which in severe cases might lead to an increase in late radiation effects. This study was planned with the objectives that reducing overall treatment time would negate the effect of accelerated repopulation and would result in better locoregional control. As with reduction in overall treatment time it is expected that patients will have more acute toxicity, therefore, to find out whether the patients will tolerate the new accelerated schedule and will they be able to finish the treatment as planned. The third of objective was that if the previous two objectives are met then in a busy setup like ours, the turnover on the machine will be much faster and in turn waiting list will be reduced.

Regarding locoregional response to RT in our study, we observed better local control both at primary and nodal site in accelerated RT arm as compared to conventional RT arm. On first follow-up, 90.9% had CR at primary site and 89.1% had CR at nodal site in accelerated arm and in conventional RT arm the corresponding figures were 81.5% and 75.9%, respectively. At a median follow-up of 43 months CR was seen in 29 patients (52.7%) in the accelerated RT arm and 24 patients (44.4%) in the conventional RT arm were able to achieve CR. Though the difference in locoregional control was not statistically significant but this study clearly indicates a trend toward improved outcome. In Danish Head and Neck Cancer Study Group (DAHANCA) study,^[8] locoregional tumor control improved significantly in the accelerated fractionation group compared with that in the conventional RT group (70% vs. 60% 5 years actuarial rate, $P = 0.0005$). There was 10% statistically significant improvement in locoregional

disease control in accelerated arm. In International Atomic Energy Agency (IAEA)-ACC study by Overgaard *et al.*,^[9] the 5-year actuarial locoregional control was 42% in the accelerated versus 30% in the conventional group ($P = 0.004$). In our study, the statistical significance could not have reached because of the smaller sample size and shorter follow-up. But our study is certainly in accordance with DAHANCA trial and IAEA-ACC study. On subset analysis, the trend of better response with accelerated fractionation was seen preferably in larynx thought it was not statistically significant. Similar to DAHANCA and IAEA-ACC study, the benefit of acceleration in this study was slightly higher for controlling advanced disease, but there was no difference in terms of control at early stage between the two schedules. At a median follow-up of 43 months, disease-free survival was higher in the accelerated radiation arm as compared to conventional one ($P = 0.09$) but there was no difference in the overall survival. Almost all treatment failures were due to insufficient locoregional tumor control. As a consequence, disease-specific survival was strongly related to insufficient locoregional control, and was therefore significantly better in patients receiving six fractions per week than for those who received five fractions per week.

We observed that acute complications were considerably more severe in the accelerated RT arm than those of conventional fractionation arm. Grade 3 mucositis were significantly higher in the accelerated arm as compared to conventional 1 (63.7% vs. 19.8%; $P = 0.001$). Moreover, the mucositis persisted longer in the accelerated fractionation arm, but all healed 3 months within the start of treatment. Similarly, Grade 3 and 4 skin toxicities were seen in significantly higher number of patients in the accelerated RT arm (72.7%) as compared to conventional arm (36.7%). Acute radiation morbidities were significantly higher with accelerated treatment in the 50–65 years of age group because they formed the major bulk of our patients which was reflected in this study. Most of the patients older than 65 years in accelerated fractionation suffered from Grade 3 acute radiation toxicities but it could not reach statistical significance because of small numbers. In our study, higher severe acute reactions seen in the accelerated RT arm were expected due to accumulated dose per week (AD) of 12 Gy in accelerated arm as compared to accumulated dose per week (AD) of 10 Gy in conventional RT arm, as acute toxicity is directly dependent on accumulated dose per week. All toxicities were effectively managed and did not lead to increased frequency of nasogastric tube feeding or treatment interruptions in the accelerated RT arm patients. Regarding acute radiation related morbidity and time taken for healing of acute reactions, our findings are comparable with DAHANCA trial, where acute radiation related morbidity was significantly higher in the accelerated RT group with a 53% frequency of a confluent mucositis compared with 33% in the conventional treatment group ($P < 0.0001$). 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. Comparable late toxicities in two groups were expected as late morbidity depends upon dose per fraction which was not different in two treatment arms, that is, 200CGy per fraction. In the DAHANCA trial and IAEA-ACC study 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 two fractionation groups. The six fractions per week schedule, resulting in a 1-week reduction in treatment time relative to conventional treatment, seems to give a good balance between improved tumor control and avoidance of excess late morbidity.

Based on our study (though it is small), DAHANCA trial and IAEA-ACC study, we feel that six fractions per week treatment is a better option as compared to five fractions per week, especially in countries where working days are 6 in a week. The conventional schedule has been evolved in West based on their working convenience rather than based on any radiobiological or scientific evidence, as they work 5 days a week. It is also clear from the trials on accelerated RT delivering seven fractions per week that 7 days treatment results into unacceptable early and late toxicities.^[10] Trials in which the acceleration has been more aggressive have resulted in unacceptable late morbidity if the total dose was not reduced.^[11] Hence, further acceleration of treatment can also not be recommended. When concurrent chemoradiation compared to accelerated RT, accelerated radiation offers a better compliance and toxicity profile already proved in prospective randomized trials.^[12] The higher incidence of acute toxicities could result in inadvertent treatment delays and prolonged overall radiation therapy treatment time. This could severely influence the outcome of RT. Overall treatment time has been observed to be one of the prime independent prognostic factors for RT response and hence any therapeutic advantage that could be expected from chemoradiotherapy could be nullified with the prolongation of overall treatment time. Such problems are more evident in patients who are nutritionally deprived and with poor general condition, as would be commonly seen in developing countries like ours. Thus, six fractions per week seem to be an ideal schedule in developing countries like ours. Moreover shortening of overall treatment time will increase the turnover on treatment machine which will help to treat more number of patients in 1-year and will reduce the waiting. Hence, shortening of overall treatment time from 6½ weeks to 5½ weeks by use of 6 fractions per week instead of 5 fractions per week is feasible, tolerable, and results in better outcome in the patients of head and neck cancers.

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Conflicts of interest

There are no conflicts of interest.

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