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Accelerated Fractionation Radiotherapy in Head and Neck Cancer: A Boon to Centers with High Patient-Resource Ratio

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Abstract
Background: *Head and Neck Squamous Cell Carcinoma (HNSCC) is a major cause of morbidity and mortality in India. Though concurrent Chemo-Radiation treatment is the standard of care, optimal radiation schedule in patients who are not fit for chemotherapy is unclear. Accelerated Fractionation Radio-Therapy (AFRT) used as an alternative, reducing overall treatment time is potentially attractive in centers with high patient-resource ratio.*
Aim: *We intended to prospectively analyze feasibility, efficacy and safety of AFRT in a public-sector teaching hospital with constrained resources. Methods: From January2013 to July2014, newly diagnosed patients with HNSCC having creatinine-clearance of <80ml/minute were screened. Radiotherapy (RT) of 66Gy in 33-fractions, 6-fractions/week was given using Cobalt60 tele-therapy machine. Toxicity evaluations were done weekly during treatment, response assessment at 6-weeks post-RT and loco-regional evaluation at scheduled follow-ups. Survival-analysis was done using Kaplan-Meir method (SPSS 20.0).*
Results: *Out of 120 patients screened, 51 were analyzed. Median age was 60-years and 44(86%) were males. Complete-Response (CR) was seen in 47(92.2%) patients. Female-gender, ECOG performance status-1, Poorly-differentiated-tumors and carcinoma-larynx showed 100% CR. At median follow-up of 12-months, 78.4% had loco-regional control. Skin reactions and dysphagia were the commonest acute-toxicities. However, all were manageable and only 6(11.8%) required treatment-breaks. At the median follow-up, Overall Survival (OS) was 80.4% (±5.6). OS was significantly related to <60 years (p=0.0293) and CR (83.3% vs 33.3%; p=0.0122). OS was inversely related to treatment-breaks (41.7%vs92.3%;p=0.0001).*
Conclusion: *AFRT, which offers decreased overall treatment time, is a fair option for high-risk HNSCCin centers with high patient-resource ratio, since there sponse and survival are good and the increased acute-toxicity is manageable. Age, Complete-Response and treatment-breaks are the major determinants of survival.*
Keywords: *AFRT, Accelerated fractionation, Head and neck squamous cell carcinoma, Head and neck cancer, HNSCC, radiotherapy.*

Introduction

Cancers of the head and neck arise from the lining membrane of the upper aero-digestive tract.[1] Ninety percent of the head and neck cancers are of squamous cell type: Head and Neck Squamous-Cell Carcinoma (HNSCC). The incidence of HNSCC is on the rise, and is now the sixth common malignant disease in the world and eighth common cause of cancer death.[2] Head and neck cancers are a common neoplasm seen in India accounting for significant morbidity and mortality.[3] Approximately 70%-80% are diagnosed as locally advanced disease, with lymph node involvement in up to 30%-50% of the cases. [4,5]

As of now, concurrent Chemo-Radiation Treatment (CRT) is the standard of care for unresectable HNSCC. [6,7,8] But the problem peeps through in patients unfit for chemotherapy, where the conventional radiation treatment alone is found to be inferior. [9,10]The optimal fractionation schedule for Radio-Therapy (RT) of HNSCC is controversial. Tumor accelerated repopulation along with poor loco-regional control and reduced survival in HNSCC led to clinical trials on newer altered fractionation schedules. [11,12] Any schedule delivering RT with a rate of dose accumulation exceeding an equivalent dose of 10Gy per week, thus shortening overall treatment time is called Accelerated Fractionation Radio-Therapy (AFRT).[13] Randomized Controlled Trials (RCT) have shown increase in loco-regional control of 10-12% and improvement in Disease Free Survival (DFS); but with increased acute toxicity and no Overall Survival (OS) advantage using AFRT. [13]

However, in centers with high patient load compared to the available RT facility, the reduction in overall treatment time by AFRT is advantageous and hence its feasibility and usefulness need to be assessed. The current study intends to prospectively analyze the effects of AFRT as the sole treatment, in patients with HNSCC who are unfit for chemotherapy, from a tertiary referral center in public sector with constrained resources.

Patients and Methods

Newly diagnosed patients with HNSCC (squamous cell carcinoma of oral cavity, oropharynx, hypo-pharynx and larynx) who presented in the department of Radiotherapy and Oncology, of a tertiary care teaching hospital in government sector, from January 2013 to July 2014 were prospectively screened for the study. Patients with stage I-IV HNSCC, age ≥18 years, Eastern Co-operative Oncology Group (ECOG) performance status 0-2 and a creatinine clearance of <80ml/minute were selected. Those who were unfit for chemotherapy constituted the target population. Patients with stage I glottis carcinoma, nasopharyngeal carcinoma, distant metastases, age >70yrs, multiple malignancies and creatinine clearance value ≥ 80 ml/minute were excluded from the study.

Pre-treatment evaluation included complete hemogram, renal and liver function tests, pan-endoscopy of upper aero-digestive tract, ultra-sonogram of neck and dental evaluation. A nasogastric tube or Percutaneous Endoscopic Gastrostomy ensured adequate nutrition in all patients. RT was given after adequate immobilization using Cobalt60 tele-therapy machine. The gross tumor volume was treated to a total dose of 66Gy in 33 fractions over 5.5 weeks (one fraction per day; six fractions a week) using lateral opposed fields and areas of potential microscopic disease to a dose of 50Gy in 20 fractions. Maximum dose to spinal cord was restricted to 44Gy.

Clinical assessment including body weight, hemogram, renal function test, tumor measurement and toxicity evaluation were done every week during the radiation and at 6weeks after completion of treatment. Acute radiation reaction of skin and mucous membrane were scored using Radiation Therapy Oncology Group (RTOG) grading[14] during weekly visits while on treatment and bi-weekly post therapy until clearance of reaction. Assessment of response to treatment was done 6weeks after treatment and was categorized to a) Complete Response (CR):

complete disappearance of macroscopic disease, b) Partial Response (PR): at least 50% decrease in the sum of perpendicular diameters of all measurable tumor masses without appearance of any fresh lesion, c) Stable Disease (SD): tumor remaining stable or decrease in size by <50% or increase in size by <25%, d) Progressive Disease (PD): increase by ≥25% of tumor size or appearance of new lesions.

The review visits were scheduled at two weekly intervals for the first three visits, monthly for next 6months and two monthly after this till last follow up. At follow up, patients underwent thorough clinical examination and ENT evaluation for loco-regional disease.

Statistics

Chi square test was used to compare qualitative variables. The Overall Survival (OS) and Disease Free Survival (DFS) curves were constructed using Kaplan-Meir method. The impact of clinico-pathological factors on DFS and OS were examined. The evaluation of differences was performed using log rank test. A 'p' value of <0.05 was considered significant. SPSS software package (version 20.0) was used to analyze the data.

Results

Between January 2013 and July 2014 a total of 120 patients were screened and 54 who met the eligibility criteria were recruited for the study. Three patients refused to give the consent. The remaining 51 patients were analyzed for the results.

Overall response

Forty-seven patients (92.2%) had complete response. Out of the four patients (7.8%) with partial response, one expired, one had salvage surgery and the remaining two patients were given chemotherapy since they had residual disease at primary site and their performance status was poor.

a) Patient characteristics and its relation with response

Most of the patients (55%) were in 51-60 age group; 94% were having ECOG performance status 2. Males predominated (86%) among recruited patients. The CR was best seen in ≤50 year age group (100%) as compared to 51-60 years (92.8%) and ≥61 years (90.5%). Female gender and ECOG performance status 1 were associated with 100% CR rates. (Table.1)

b) Tumor characteristics and its relation with response

Majority of patients recruited were having carcinoma larynx (37%) or carcinoma oral cavity (25%). (Figure.1) Advanced disease (Stages III&IV) accounted for a total of 92% of recruited cases. CR rates were 100% for stages I&II, 95.8% for stage III and 87% for stage IV HNSCC. Poorly differentiated tumors showed 100% CR. Response was best in carcinoma larynx (100%) and worse in carcinoma hypo-pharynx (89%). (Table.2)

c) Treatment related factors and its relation to response

Twelve-patients (23.5%) had treatment breaks, the cause being grade-3 radiation reaction in six patients. Remaining six patients were unfortunate to have radiation machine failure. CR rates were comparable in patients with and without treatment breaks (91.6% vs 95.0%)

Events on follow-up

Forty patients (78.4%) had loco-regional control during the follow-up period. Eight patients (15.7%) developed failure at primary site, out of which five expired. Two had nodal failure and one had failure at primary and nodal sites.

Acute toxicity

Radiation induced acute toxicities (Figure.2) were graded based on RTOG grading system.[14]All patients experienced grade-2&3 skin reactions.No grade-4 reactions were seen. Dysphagia grade-3 was seen in 53% while 33% had grade-3

dysphonia. Grade-2 xerostomia was seen in 53% and 37% developed grade-2 ototoxicity (external otitis). Hematological toxicity expressed in the form of a decrease in hemoglobin to ≤10g% (grade-1) was present in all patients; 63% had grade-1 and 37% had grade-2 leucopenia. Overall, acute toxicities were manageable; only six patients (11.8%) required treatment break and hospitalization.

Survival Analysis

At the median follow-up of 12 months, overall survival (OS) was 80.4% (standard error 5.6). (Figure.3) The OS probability was 90% for those who are below the age of 60 years compared to 66.7% for those ≥60 years (p= 0.0293). The survival was significantly less in patients with treatment breaks (41.7% vs 92.3%, p= 0.0001). Patients with complete response (CR) had better overall survival than those with partial response (83.3% vs 33.3%; p=0.0122). Gender (p=0.0951), primary tumor status (p=0.9991), nodal status (p=0.0546) and stage of disease (p=0.2859) were not significantly related to OS. The disease free survival (DFS) at one year was 82.5% (standard error 5.7) and the projected two-year probability of DFS was 70.9%. Treatment breaks had significant negative effect on DFS (44.4% vs 91.6%, p=0.0012). (Figure.4) DFS was not significantly related to age (p=0.9338), gender (p=0.0759), primary tumor status (p=0.1073), nodal status (p=0.0686), stage of disease (p=0.3827) or CR rate (p=0.0784)

Table.1: Relation between patient characteristics and Complete Response (CR)

	No. Patients	Percentage of total	CR Rate (%)
Age (years)			
≤ 40	1	2	100
41-50	1	2	100
51-60	28	55	93
>60	21	41	90
Gender			
Male	44	86	93
Female	7	14	100
ECOG Performance			
1	1	2	100
2	48	94	93.75
3	2	4	100

Table.2: Relation between tumor characteristics and Complete Response (CR)

Tumor Characteristics	No. Patients	Percentage of total	CR Rate (%)
Anatomical Sub-sites			
Hypopharynx	9	18	89
Larynx	19	37	100
Oral Cavity	13	25	92
Oropharynx	10	20	90
Primary Tumor Status			
T1	5	10	100
T2	16	31	94
T3	21	41	95
T4	9	18	88
Regional Lymph node Status			
N0			
N1	17	33	95
N2	18	35	100
N3	15	30	93
	1	2	0
Composite Stage			
I	1	2	100
II	3	6	100
III	24	47	95
IV	23	45	86
Grade of Tumor			
Poorly Differentiated	2	4	100
Moderately Differentiated	31	61	97
Well Differentiated	18	35	11

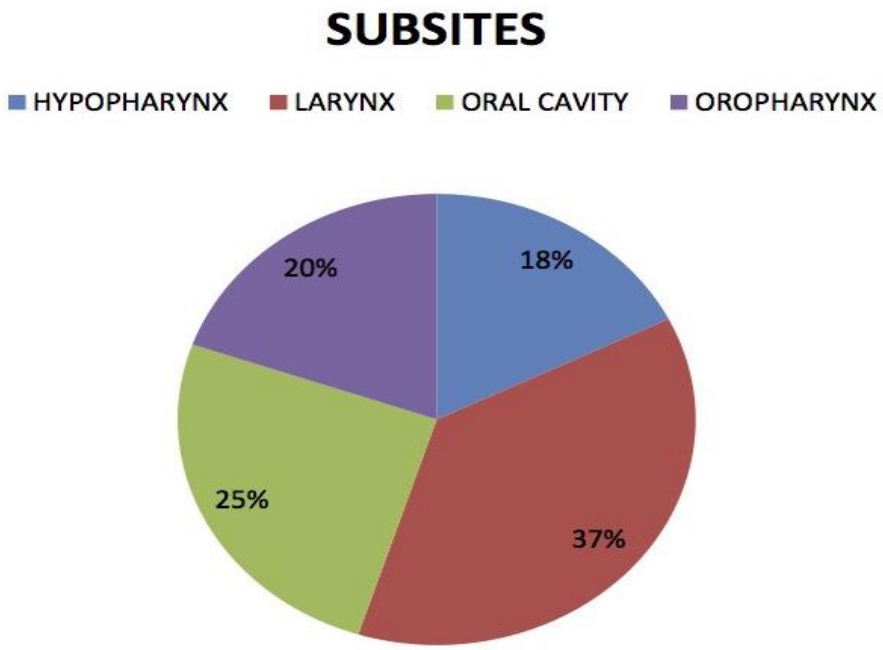

Figure.1: Tumor sub-site distribution in study population

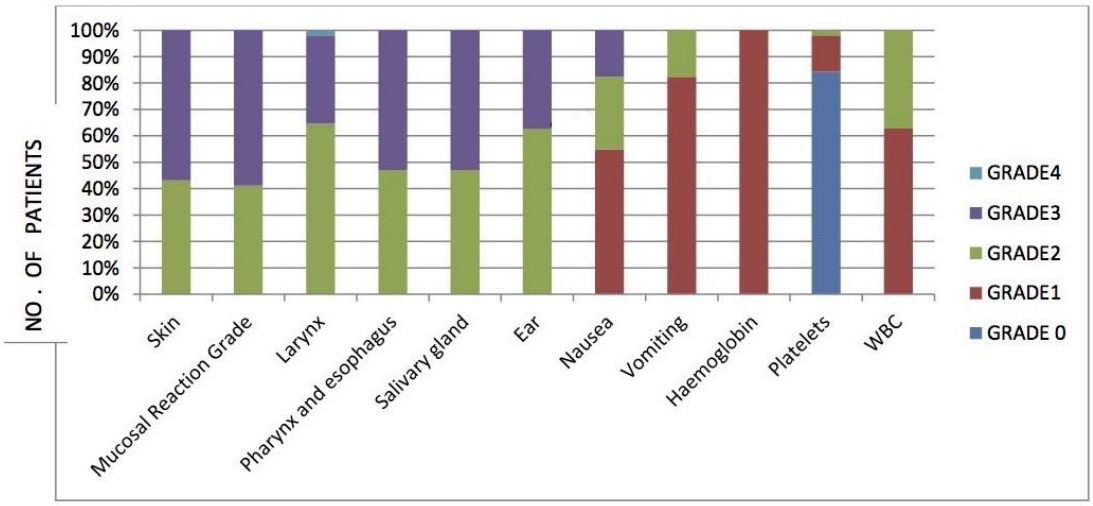

Figure.2: RTOG grading of acute toxicity following radiation

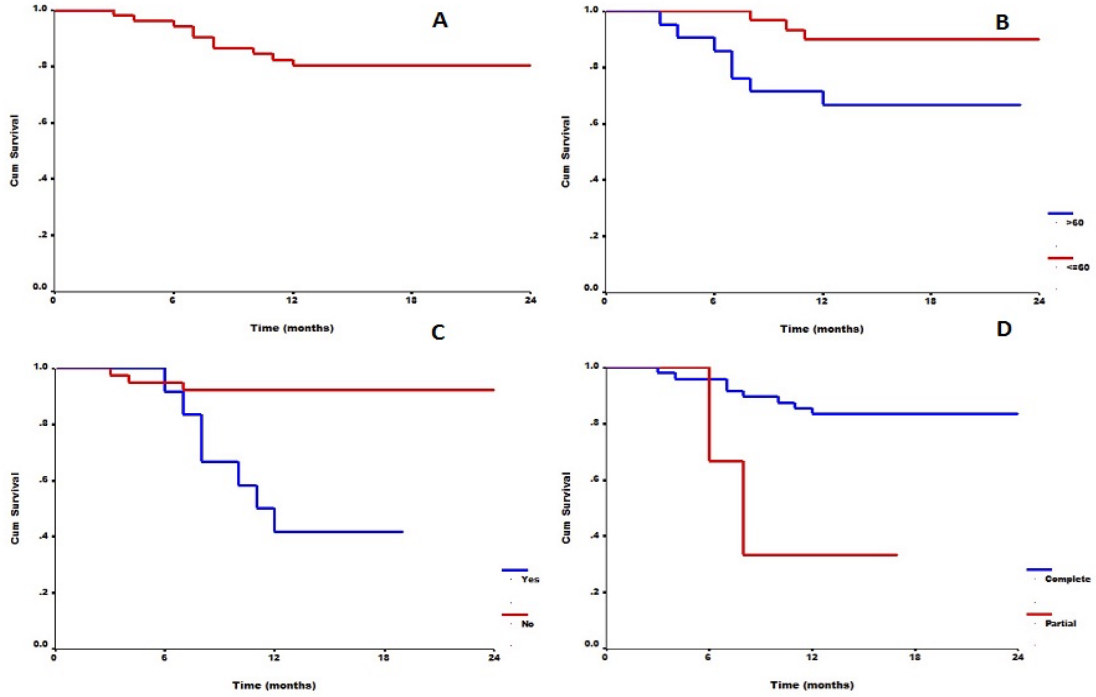

Figure.3: Kaplan-Meier plots showing A) Overall Survival, B) Overall Survival by age, C) Overall Survival by treatment breaks and D) Overall Survival by response

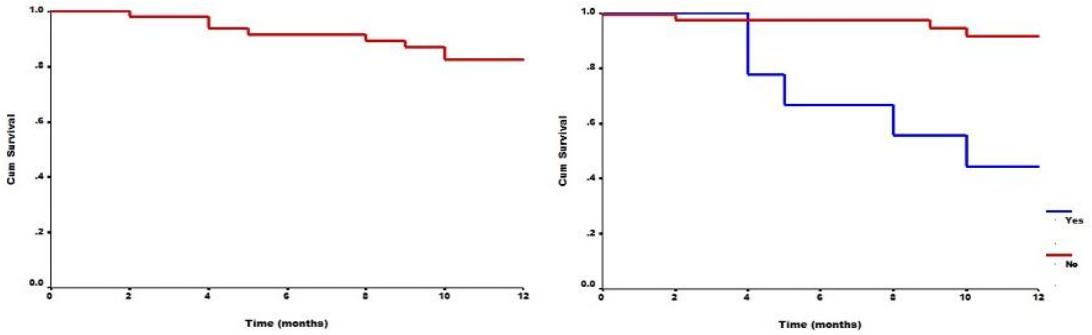

Figure.4: Kaplan-Meier plots showing A) Disease Free Survival, B) Disease Free Survival by treatment breaks

Discussion

From a radiobiology perspective, it is known that after a certain period of RT called the lag phase, resistant tumor clonogens start accelerated repopulation.[15] So a dose increment, especially during the final phase of radiation treatment is needed to achieve tumor control. Therefore the rationale for accelerated fractionation is to counter the accelerated repopulation.[11,12,15]Two types of accelerated fractionation schedules exist. [15] The first group is pure AFRT regime where overall treatment time is reduced without concurrent changes in fraction size or total dose. The present study belongs to this group, where the overall treatment time was reduced by a week. In the second group there exists changes in fraction size, total dose and time distribution. This group is again divided to three types: type A (intensive short course treatment), type B (split course twice daily treatment) and type C (concomitant boost treatment).

Two major trials exist with regard to pure AFRT schedule. In the largest trial (DAHANCA 6 and 7 study),[13]1476 patients were randomized to arm-I AFRT schedule of 6 fractions per week and arm-II conventional RT schedule of 5 fractions per week. The patients received a total of 66-68 Gy in 33-34 fractions. In a similar trial by Overgaard et al. (IAEA-ACC study),[16]900 patients were randomized to AFRT group and conventional RT group. A total dose of 66-70Gy in 33-35 fractions were given in both groups.

The CR rate of 92.2% in the current study was comparable to results of DAHANCA (85%) and IAEA-ACC trials (72%).[13,16] Young age, female gender and good performance status showed 100% CR. Like wise, early stage disease, poorly differentiated tumor and carcinoma of the larynx were associated with cent percent response. The loco-regional control was 78.4% at median follow-up of 12-months. Overall Survival (OS) was 80.4% at one year with significantly better survival in younger people (<60 years) and those with complete response to treatment. The DFS of 82.5% at 12-months in the current study goes hand-in-hand with a one year DFS of 84% in DAHANCA trial[13] and 75% in IAEA-ICC trial.[16]None of the patient related and tumor related factors showed significant correlation with DFS.

The treatment break showed significant inverse relation with overall and disease free survival, though complete response rates were not much different in those with and without treatment breaks (91.6% vs 95.0%). Breaks in treatment occurred in approximately a quarter of patients; half of them due to acute toxicity and the other half due to machine breakdown while on treatment. Regarding toxicity profile, acute toxicity was higher compared to the previous two major studies.[13,16]Still only 11.8% needed treatment break and hospital admission due to the toxicity of treatment.

Thus the response to treatment, events on follow-up and the survival parameters in the current study are comparable to other major trials on AFRT. [13,16] Though acute toxicity was higher in our study, they were manageable. To the best of our knowledge, at present there are no head-to-head comparison studies of AFRT with standard chemo-radiotherapy in the treatment of HNSCC. However, the loco-regional control rate of 78.4% at 12-months in the current study is comparable with 75% loco-regional control at one year in the RTOG 9501/intergroup phase III trial, using the best possible combination of surgery, chemotherapy and radiotherapy.[17]

Age of patients, complete response to treatment and the treatment break were the major determinants of the outcome. Out of these factors, the significant negative impact of treatment break requires special emphasis since it is at least partially avoidable. Half of the treatment break was due to acute toxicity, which is expected in AFRT regime.[13,18]However, the other half was due to radiation machine failure which was very unfortunate and avoidable. This may not be uncommon in resource-poor public sector facilities.

To sum up, AFRT schedule is a fair alternative compared to conventional fractionation radiotherapy in HNSCC in view of a) radiobiological advantage of countering accelerated repopulation b) decreased overall treatment time c) manageable toxicity profile d) comparable outcome with the current standard of care. In developing countries like India with high population density and increased number of HNSCC compared to poor RT facilities, AFRT offers an advantage.[19]The reduction of overall treatment time allows more patients to be treated with available resources.[19]Carefully designed randomized control trials with large number of patients and long follow-up are needed in future to clarify these results and to look for feasibility of combining AFRT with chemotherapy in patients with HNSCC.

Conclusion

Accelerated Fractionation Radiotherapy in the form of six fractions per week is feasible and fairly well tolerated as a sole treatment in high-risk patients with head and neck squamous cell carcinoma. Younger age, complete response to treatment and absence of treatment break are the major determinants of survival. Though high skin and mucosal reactions contribute to the treatment breaks, radiation machine failure remains a major and avoidable cause. In centers with high patient-resource ratio, accelerated fractionation schedule help providing treatment to more patients without altering the treatment efficacy. Future trials will be able to address the question of late toxicity and extended survival rates.

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