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Original Research Paper

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# A COMPARATIVE PROSPECTIVE STUDY BETWEEN STANDARD AND ALTERED FRACTIONATED RADIOTHERAPY FOR LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA

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## ABSTRACT

**Background and Purpose:** To compare conventionally fractionated chemoradiotherapy (CF-CRT) with two variants of altered fractionated radiotherapy (AFRT) in patients with locally advanced head and neck squamous cell carcinoma (LAHNSCC). **Material and Methods:** 64 patients diagnosed with LAHNSCC were randomized either to receive CF-CRT (70 Gy/35 fractions) in Arm-I or hyper-fractionation radiotherapy (HFRT 81.6 Gy/68 fractions 1.2 Gy BID) in Arm-II or concomitant boost radiotherapy (CBT 71.6 Gy/28 fractions with last 16 fractions BID as concomitant boost) in Arm-III. 35mg/m2 cisplatin weekly was given as concurrent chemotherapy regimen in Arm-I. The primary objective was to assess acute toxicity, and the secondary endpoint was the radiotherapeutic response between CF-CRT and AFRT. Radiation Therapy Oncology Group (RTOG) criteria were used for evaluating acute toxicity. Response Evaluation Criteria In Solid Tumor 1.1 (RECIST 1.1) was used to assess response. **Results:** Twenty-two, 21, and 21 patients were randomly assigned to Arm-I, II, and III. The treatment was completed by 22, 17, and 18 patients in Arm-I, II, and III. The acute Grade-II skin toxicity was higher in Arm-II (58.8%) and III (50.0%) compared to Arm-I (36.3 %), but the correlation was insignificant (p- .17). Acute Grade-III mucosal toxicity was higher in Arm-II (35.2%) and III (38.8%), and it shows a trend towards significance (p- .059). Arm-II had higher complete responder (52.9%) compared to Arm-I (27.2%), and the correlation was insignificant (p- .23). **Conclusion:** The AFRT arms II and III showed similar radiotherapeutic response as CF-CRT arm. Comparable acute toxicities were seen in all arms except for the mucosal toxicity, which was higher in Arm-II and III.

**KEYWORDS :** Head and neck squamous cell carcinoma, conventionally fractionated chemoradiotherapy, altered fractionated radiotherapy, hyper-fractionated radiotherapy.

## BACKGROUND:

Head and Neck Squamous cell carcinoma (HNSCC) is the seventh most common malignancy worldwide. Incidence in male and female was 0.66 and 0.22 million cases per annum in 2018.[1] In India, the incidence rate of HNSCC was 0.20 million cases per annum, and mortality rate was 0.12 million cases per annum in 2018.[2]

The radiotherapy with curative or palliative intent or as part of multimodality management was the mainstay of treatment in nearly 75% of HNSCC.[3] Conventional fractionated radiotherapy (CFRT) with 1.8-2.0 Gray per fraction resulted in better disease local control (LC) and lesser tissue complication.[4] The prognosis of locally advanced HNSCC (LAHNSCC) patient is poor with 5-year overall survival (OS) of 40-50% with CFRT.[5] Accelerated repopulation of a clonogenic tumor cell is one of the principal cause of treatment failure in HNSCC, and it usually starts around the fourth week of radiation. The extra daily dose of 0.6 Gy is needed to combat this repopulation. The AFRT decrease the disease local failure rate and increase survival by maximizing the therapeutic ratio.[6] Many randomized clinical studies with modified fractionation regimen have resulted in better locoregional control (LRC) and OS in contrast to CF.[7–9]

In HNSCC, CF-CRT with concurrent three weekly cisplatin chemotherapy of dose 100mg/m$^2$ is a standard regimen, and recent studies and meta-analysis have reported better LRC and OS when compared with CF.[10] To date, there is no definitive consensus guideline regarding optimal treatment therapy for the management of advanced HNSCC, with a higher preference given towards CF-CRT. The treatment is based on the patient's performance status, disease stage, clinical expertise, and geographic treatment management preference. Based on these results; we conducted a comparative randomized prospective single institutional based study between CF-CRT and AFRT regimen in LAHNSCC to assess the acute toxicity profile and radiotherapeutic response in the Indian population.

## AIM:

The primary objective was to evaluate acute toxicity, and the secondary endpoint was the radiotherapeutic response in different fractionated radiotherapy to treat locally advanced head and neck squamous cell carcinoma (LAHNSCC)

Materials and Methods: This single Institutional, randomized comparative prospective research study was performed from February 2018 till April 2019. The Ethical Committee of the hospital approved the study. Information regarding the protocol was given to all volunteer patients, and they signed informed consent. Sixty-four patients with pathologically proven head and neck squamous cell carcinoma (HNSCC) (oropharynx, hypopharynx, and larynx) were enrolled from February 2018 to January 2019. The inclusion basis was the age of ≥18 and <75 years, the Karnofsky performance score of ≥70, stage III-IVB, adequate differential blood count and complete blood count with hemoglobin ≥ 12 mg/dl, neutrophils > 1.5 x 10$^9$ cells per liter, platelets >100 x 10$^9$ cells per liter, normal kidney function with creatinine clearance of ≥ 50 ml per minute, and normal liver function. Direct laryngoscopy and contrast-enhanced computed tomography (CECT) of the head and the whole neck was done to recognize the loco-regional disease status. The American Joint Committee on Cancer (AJCC 7$^{th}$ edition; 2010) was used for TNM staging in this study.[11] The enrolled patients were randomly assigned into three arms using computer-generated numbers.

## Proposed methodology:

Contrast-enhanced computed tomography (CECT) simulation was done with three-point fixation thermoplastic cast immobilization. Planning images (both plain and contrast) of 3mm were generated by scanning the patient on Phillips 16 slice CT simulator. The data was then transmitted to the treatment planning system (TPS- Monaco Sim Integrated Planning System Version. 10) using Digital Imaging and Communications in Medicine (DICOM) protocol 3.0.

The target volumes and organs at risk were contoured as per the International Commission on Radiation Units and measurements report number 50 and 62.[12,13]

The radiation dose was delivered using a shrinking field technique for all Arms.

## Arm-I (n=22):

A dose of 70Gy over 7 weeks (2Gy/fraction, 5days/week) was planned with weekly intravenous 35mg/m$^2$ cisplatin. In phase-I, the dose of 44Gy was delivered using parallel opposed lateral face and neck field and a low anterior neck (LAN) field.

The phase-II was delivered using opposed lateral face and neck field sparing spinal cord up to a cumulative dose of 60Gy followed by a boost dose of 10Gy to primary disease in the third phase.

**Arm-II (n=17):**
A dose of 81.6Gy over 7 weeks (1.2Gy/fractions, two fractions/day with an interval of more than 6 hours between 2 fractions, 5days/week) was planned. In phase-I, the dose of 48Gy in 40 fractions was delivered using parallel opposed lateral face and neck field and a LAN. The phase-II was delivered using lateral parallel opposed face and neck field sparing spinal cord up to a dose of 69.6Gy followed by a boost of 12Gy in 10 fractions to primary disease in the third phase.

**Arm-III (n=19):**
The dose of 71.6Gy over 6 weeks (1.7Gy/fraction, 5 fractions/week) was planned. In phase-I, a dose of 47.6Gy in 28 fractions was given by lateral parallel opposed face and neck field and a LAN. The phase-II of 15Gy over 10 fractions (1.5Gy/fraction) was delivered using lateral parallel opposed face and neck sparing spinal cord up to a cumulative dose of 62.6Gy followed by a boost dose of 9Gy in 6 fractions to primary disease in phase-III. The phase-II and phase-III was delivered along with phase-I in the evening with a gap for more than 6 hours between two fractions during the last 16 treatment days.

The treatment plan was implemented on a linear accelerator (Synergy; Elekta). The orthogonal pair (Antero-posterior (AP) and right-lateral (Lat)) of single exposure electronic portal image (EPI) were obtained using Elekta Perkin Elmer AL type panel EPI device (Elekta Medical System) after positioning of the patient for set-up and target reproducibility. For every patient, EPI was done on Day1, Day2, Day3 of 1st week and the first day of subsequent weeks.

Three months after completion of CRT, the radiotherapeutic response was evaluated by clinical examination, direct laryngoscopy, and the head and whole neck CECT or magnetic resonance imaging. In a clinically suspicious case, FDG-positron emission tomography was done. RECIST 1.1 criteria were used to determine the radiotherapeutic response, and it divided the patient response into complete responder (CR), partial responder (PR), stable disease (SD), and a progression of disease (PD).[14] During treatment, each patient was assessed weekly by the treating physician for acute toxicity and was recorded using criteria defined by the Radiation Therapy Oncology Group (RTOG).[15]

**Statistical analysis:**
The affiliation between acute toxicity grade, radiotherapeutic response with the treatment Arms-I, II, and III were assessed using the Chi-square test $c^2$ or Fisher's exact test. The p-values reported are two-tailed, and p- < .05 is regarded as statistically significant. IBM SPSS Version 21 software was used to perform the statistical analysis.

## RESULTS:
The study flowchart from patient assessment to enrollment in three different fractionated radiotherapy arms and treatment evaluation are shown in Figure 1. Four patients defaulted in Arm-II, and 3 patients defaulted in Arm-III within 1-3 weeks of initiation of radiotherapy because of personal and social problems. The median age of the cohort was 52 years (range 37-72 years) Demographic and disease characteristics of the patients, are stated in Table 1. Baseline characteristic were comparable among the three arms.

The estimated time of completion of treatment was 7 weeks in Arm-1, Arm-II and 6 weeks in Arm-III, but only 20.0% of patients in Arm-II completed treatment within the expected time in comparison to 86.4% in Arm-1 and 82.4% in Arm-3 as shown in Figure 2 (A). Grade-IV skin toxicities were much higher in AFRT arms in comparison to CF-CRT Arm with 17.7% in Arm-III, 23.5% in Arm-II, and 9.1% in Arm-I. The proportion of Grade-III mucositis was noticed higher in AFRT arms with 26.8% in Arm-III, 35.3% in Arm-II, and 18.1% in Arm-I and the correlation shows a trend towards significance (p- 0.059) as stated in Table 2. The proportion of anemia and neutropenia were also higher in AFRT arms, but it was statistically insignificant, as shown in Table 2.

Majority of patients showed PR, 54.55% in Arm-I, 41.18% in Arm-II, and 61.11% in Arm-III. 3 patients (13.6%) was noticed with SD in Arm-1, whereas no SD was seen in Arm-II and III. No PD was noticed in Arm-II. The proportion of CR was 52.9% in Arm-II, whereas in Arm I and Arm-III CR rate was 27.2% and 27.7%, but the affiliation was statistically insignificant (p-0.23) as shown in Table 3 and Figure 2 (B). .

## DISCUSSION:
The resulf of our research study show that the HF treatment of LAHNSCC has a better radiotherapeutic response in comparison to CF-CRT and CBT. CF-CRT and CBT have a similar radiotherapeutic response but with higher acute toxicity in CBT. HF was also associated with higher acute toxicities as compared to CF-CRT.

The radiotherapeutic response in this present study was observed to be better for Arm-II (CR-52.94%, PR- 41.18%, PD-0%) as compared to Arm-I (CR- 27.2%, PR- 54.5%, PD- 4.5%) but the correlation was statistically insignificant. In studies by Sanchiz F *et al.*, Horiot JC *et al.*, and Pinto LHJ *et al.* similar radiotherapeutic response was reported.[16–18]

The radiotherapeutic response in this study was observed to be (CR- 27.7%, PR- 61.1%, PD- 5.5%) for Arm-III as compared to Arm-I (CR- 27.2%, PR- 54.5%, PD- 4.5%). A study by Sanguineti *et al.* randomized patients post-surgery to conventional 60 Gy in six weeks versus 64 Gy in five weeks with twice daily radiation treatment delivered in the first and last week, and no difference was noticed in radiotherapeutic response between the two arms.[19]

The Grade-III mucositis in Arm-III of our study was 35.2% as compared to 18.1% in Arm-I. The study by Ghoshal S *et al.* randomized patients into standard CF regimen versus CBF regimen in LAHNSCC, and similar Grade-III mucositis (19.0% in CF Arm *vs.* 35.0% in CBF Arm) were observed.[20]

Some of the limitations of our study are we used 35mg/$m^2$ cisplatin weekly during CF-CRT as per institutional protocol, whereas, a large number of randomized studies have used 100mg/$m^2$ three weekly during CRT in advanced HNSCC. Hence, using 35mg/$m^2$ of weekly cisplatin might have resulted in lower grade> 2 toxicity and lesser treatment response in Arm-I in our study. Another limitation was a small patient number, as the larger patient number is needed to estimate notable radiotherapeutic response rate, and acute toxicity.

The prospective multi-institutional randomized cohort study with survival, disease progression, locoregional control, and late toxicity data of this radiotherapy regimen will be required for any recommendation in the relative clinical management of such cases.

In conclusion, HF is associated with better radiotherapeutic response in LAHNSCC as compared to CF-CRT and CBT. However, it is affiliated with higher but manageable acute toxicities. The evaluation of this regimen on a larger patient population in a randomized prospective setting is also recommended to authenticate the concepts further.

**Table 1: Patient characteristics**

| Patient characteristics | Arm I (n=22) | Arm II (n=17) | Arm III (n=18) |
|---|---|---|---|
| Age (y/o) | | | |
| ≤60 | 15 (68.2%) | 6.0 (35.3%) | 10.0 (55.6%) |
| >60 | 7.0 (31.8%) | 11.0 (64.7%) | 8.0 (44.4%) |
| Performance score (KPS) | | | |
| 70-80 | 4.0 (18.2%) | 8.0 (47.1%) | 3.0 (16.7%) |
| 80-90 | 17 (77.3%) | 8.0 (47.1%) | 13 (72.2%) |
| 90-100 | 1.0 (4.5%) | 1.0 (5.9%) | 2.0 (11.1%) |
| Sex | | | |
| Male | 18.0 (81.8%) | 16.0 (94.1%) | 14.0 (77.8%) |
| Female | 4.0 (18.2%) | 1.0 (5.9%) | 4.0 (22.2%) |
| Site of disease | | | |
| Oropharynx | 12 (54.5%) | 5.0 (29.4%) | 6.0 (30.3%) |
| Hypopharynx | 1.0 (4.5%) | 0.0 (0.0%) | 1.0 (5.5%) |
| Larynx | 9.0 (40.9%) | 12.0 (70.5%) | 11.0 (61.2%) |
| Clinical stage† | | | |
| Stage III | 16.0 (72.7%) | 12.0 (70.6%) | 7.0 (38.9%) |
| Stage IVA-B | 6.0 (27.3%) | 5.0 (29.4%) | 11.0 (61.1%) |
| Differentiation | | | |
| WDSCC | 5.0 (22.7%) | 11.0 (64.7%) | 9.0 (50.0%) |
| MDSCC | 17.0 (77.3%) | 6.0 (35.3%) | 8.0 (44.4%) |
| PDSCC | 0.0 (0.0%) | 0.0 (0.0%) | 1.0 (5.6%) |

Note: Data are number (%). Abbreviations: KPS = Kernofsky performance score; WDSCC= well differentiated squamous cell carcinoma; MDSCC = moderately differentiated squamous cell carcinoma; PDSCC = poorly differentiated squamous cell carcinoma

† Staging was done as per American Joint Committee on Cancer Guideline (AJCC 7th Edition manual; 2010)

**Table 2: Acute toxicity comparison between Arm I, II and III**

| Acute toxicity† | Arm-I (n=22) | Arm-II (n=17) | Arm-III (n=18) | p-value |
|---|---|---|---|---|
| Skin Toxicity | | | | 0.174 |
| Grade-I | 3.0 (13.6%) | 0.0 (0.0%) | 0.0 (0.0%) | |
| Grade-II | 8.0 (36.3%) | 10 .0(58.8%) | 9.0 (50.0%) | |
| Grade-III | 9.0 (40.9%) | 3.0 (17.6%) | 4.0 (22.2%) | |
| Grade-IV | 2.0 (9.1%) | 4.0 (23.5%) | 5.0 (27.7%) | |
| Mucosal Toxicity | | | | 0.059 |
| Grade-I | 7.0 (31.8%) | 1.0 (5.8%) | 0.0 (0.0%) | |
| Grade-II | 11.0 (50.0%) | 9.0 (52.9%) | 10.0 (55.5%) | |
| Grade-III | 4.0 (18.1%) | 6.0 (35.2%) | 7.0 (38.8%) | |
| Grade-IV | 0.0 (0.0%) | 1.0 (5.9%) | 1.0 (5.5%) | |
| Anaemia | | | | 0.950 |
| Grade-I | 4.0 (18.1%) | 5.0 (29.4%) | 4.0 (22.2%) | |
| Grade-II | 1.0 (4.5%) | 2.0 (11.7%) | 2.0 (11.1%) | |
| Grade-III | 0.0 (0.0%) | 1.0 (5.8%) | 2.0 (11.1%) | |
| Grade-IV | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | |
| Neutropenia | | | | 1.0 |
| Grade-I | 2.0 (9.1%) | 2.0 (11.7%) | 2.0 (11.1%) | |
| Grade-II | 1.0 (4.5%) | 1.0 (5.8%) | 1.0 (5.5%) | |
| Grade-III | 0.0 (0.0%) | 0.0 (0.0%) | 1.0 (5.5%) | |
| Grade-IV | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | |

Note: Data are number (%).

† Acute toxicity profile was evaluated using Radiation Therapy Oncology Group Criteria (RTOG)

**Table 3: Comparison of Treatment response between Arm I, II, and III**

| Radiotherapeutic response† | Arm-I (n =22) | Arm-II (n = 17) | Arm-III (n = 18) | p-value |
|---|---|---|---|---|
| Complete response | 6.0 (27.2%) | 9.0 (52.9%) | 5.0 (27.7%) | 0.231 |
| Partial response | 12.0 (54.5%) | 7.0 (41.1%) | 11.0 (61.1%) | |
| Progression of disease | 1.0 (4.5%) | 0.0 (0.0%) | 1.0 (5.5%) | |
| Stable disease | 3.0 (13.6%) | 0.0 (0.0%) | 0.0 (0.0%) | |

Note: Data are numbers (%)

† Radiotherapeutic response was evaluated using Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1; 2009)

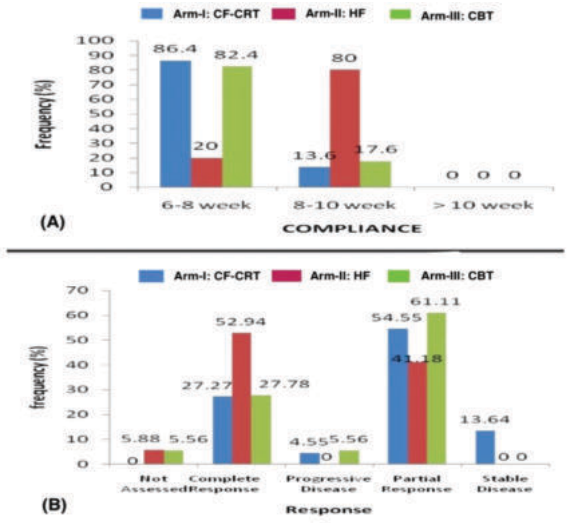


**Figure 1: Comparison of treatment compliance (A) and radiotherapeutic response (B) between CF-CRT, HF, and CBT treatment arms.**

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