# Comparative Evaluation of Quad Shot versus Twice Weekly Palliative Radiotherapy for Locally Advanced Head and Neck Cancer

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**ABSTRACT**

**BACKGROUND**

Majority of Head and Neck Squamous Cell Cancer patients in India present in advanced stages. They are not candidates for multimodality treatment due to locoregionally advanced disease, poor performance status or distant metastasis. Hypo-fractionated regimens have been used for palliation of locally advanced head and neck cancers. Here we aim to compare two different schedules of palliative radiotherapy to evaluate and compare their feasibility, efficacy, tolerability, local control and side effects.

**METHODS**

This is a prospective, randomized study, conducted among 60 untreated patients of head and neck squamous cell carcinoma where palliative radiotherapy was indicated. These patients were divided in to two groups of 30 patients each by computer generated randomization. In Group 1, 14.8 Gy/ 4 fractions/ 2 days (2 fraction per day 6 hours apart for 2 consecutive days) repeated for 2 more cycles each with an interval of 3 weeks. In Group 2, 32 Gy/ 8 fractions/ 2 days (2 fraction per day 6 hours apart twice weekly (Wednesday and Saturday) for 4 consecutive weeks).

**RESULTS**

Group 1 had slightly better locoregional control but the difference was statistically insignificant. Group 1 had more grade 1 skin and mucosal reaction than group 2. Group 2 had more grade 2 skin and mucosal reaction than group 1. Symptomatic relief (subjective regression) was better in group 1 than group 2.

**CONCLUSIONS**

Both quad shot and twice weekly palliative radiotherapy for locally advanced head and neck cancer are comparable in term of efficacy, toxicity and feasibility.

**KEYWORDS**

Head and neck cancers, locally very advanced, palliative radiotherapy

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## BACKGROUND

Newly diagnosed cases of head and neck cancer (2018): 4.9% of all cancers worldwide & 15.2% of all cancers in India and deaths: 4.8% of all cancer deaths worldwide & 15.6% of all cancer deaths in India.[1] Head and neck cancers account for 41.2% of all cancers seen in Department of Radiation Oncology, Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak, in the year 2016.[2] Majority of Head and Neck Squamous Cell Cancers in India present in advance stages and are not candidates for multimodality treatment due to loco-regionally advanced disease, poor performance status or distant metastasis. Traditionally, hypo-fractionated regimens have been used for palliation of locally advanced head and neck cancers[3]. Due to radiobiological advantages (large dose per fraction), shorter overall treatment time and Logistical convenience and limited life expectancy in this group of patients.

We wanted to evaluate and compare feasibility, efficacy, tolerability, local control and side effects of two palliative radiotherapy schedules in locally advanced inoperable head and neck carcinoma.

## METHODS

The study was conducted on 60 untreated patients of head and neck squamous cell carcinoma where palliative radiotherapy was indicated. These patients were divided in two groups of 30 patients each by computer generated randomization. In GROUP 1, 14.8 Gy/ 4 fractions/ 2 days (2 fraction per day 6 hours apart for 2 consecutive days) repeated for 2 more cycles each with an interval of 3 weeks[4]. In GROUP 2, 32 Gy/ 8 fractions/ 2 days (2 fraction per day 6 hours apart twice weekly (Wednesday and Saturday) for 4 consecutive weeks). All the patients were treated in a supine position. The patients were treated by parallel opposing fields and the dose were prescribed to the mid plane at the central axis. Radiotherapy were delivered by Cobalt-60 using the fields generated as above. From the commencement of treatment, all the patients included in the study were carefully and regularly assessed weekly during treatment and at completion of treatment. Detailed clinical evaluation for the tolerance of each patient to the delivered treatment were done by thorough local examination of the patient for local disease status along with observation of acute toxic side effects of radiation. Radiation reactions were assessed by Radiation Therapy Oncology Group (RTOG) criteria and WHO toxicity criteria. Radiation Therapy Oncology Group (RTOG) acute morbidity scoring criteria are relevant from day 1, the commencement of radiation, through day 90 and thereafter, the RTOG criteria for late effects are to be utilized. Tumour response (both primary and nodal response) were assessed by WHO response criteria. All the patients were followed up regularly on OPD basis for a period of at least six months, weekly for four weeks in first month and then monthly. At every visit, each patient were clinically evaluated for local control of disease and treatment related complications. The patients were assessed for any evidence of distant metastasis during each follow up. The data thus obtained were entered in MS-Excel 2010 and percentage proportion were calculated. Chi-square test, unpaired t test and paired t test were applied to test the significance of the results using SPSS (Statistical Package for Social Sciences) software version 20.

**Inclusion Criteria**

- Karnofsky Performance Status >60.
- Complete haemogram with Hb>8 gm/dL; TLC>4000/cmm, Platelet count >100,000/cmm.
- Renal function tests with Blood urea <40 mg/dL and Serum creatinine < 1.5 mg/dL.
- Liver function tests with SGOT <35 IU/L and SGPT <40 IU/L.
- AJCC stage III/IV and a positive biopsy for squamous cell carcinoma of head and neck.
- Patients who sign the informed consent and are ready to be on follow up as required.

**Exclusion Criteria**

- Distant metastases.
- Prior radiation, surgery or chemotherapy for the disease.
- A poor general condition with Karnofsky Performance Status of <60.
- Pregnant or lactating patient.
- Associated medical condition such as renal disease, liver disease or heart disease.
- Patients having a primary in thyroid / salivary glands.
- Histopathology other than squamous cell carcinoma.

| Patient Characteristics | Group 1(n=30) | Group 2(n=30) |
|---|---|---|
| Mean age at presentation | 56.36 years | 59.06 years |
| Gender wise distribution | All patient were male | 24 patients were male and 6 patients were female |
| Rural status (%) | 28/30 (93.3%) | 27/30 (90%) |
| Urban status (%) | 02/30 (6.7%) | 03 (10%) |
| Smoking status (%) | 25/30(83.33%) | 25/30(83.33%) |
| Alcohol habit status (%) | 16/30(53.33%) | 14/30(46.67%) |
| Chief complaint at the time of presentation (%) | Difficulty in swallowing was the most common symptom in group 1 (43.33%) | Pain in throat (46.67%) |
| Karnofsky Performance Status (>70) | 17/30 (56.67%) | 16/30(53.3%) |
| Histopathological distribution (Most common) | Moderately differentiated squamous cell (100%) | Moderately differentiated squamous cell (73.3%) |
| Tumor morphology (Most common) | Ulceroproliferative (83.33%) | Ulceroproliferative (66.67%) |
| TNM Stage wise distribution at presentation (Most common) | Stage IV (96.7%) | Stage IV (90%) |

## RESULTS

**Group 1 vs. Group 2**

- Mean age at presentation: -56.36 years vs. 59.06 years.
- Gender wise distribution (male): -100% vs. 80%).
- Rural status (%): -93.3% vs. 90%.
- Urban status (%) 6.7% vs. 10%.

- Smoking status (%): -83.33 vs. 83.33.
- Alcohol habit status (%) 53.33% vs. 46.67%
- Chief complaint at the time of presentation (%) difficulty in swallowing (43.33%) vs. pain in throat (46.67%)
- Karnofsky Performance Status (>70) 56.67% vs 53.3%
- Histopathological distribution (Most common) moderately differentiated squamous cell (100%) vs. moderately differentiated squamous cell (73.3%).
- Tumour morphology (Most common) Ulceroproliferative (83.33%) vs. Ulceroproliferative (66.67%)
- TNM Stage wise distribution at presentation (Most common) Stage IV (96.7%) vs. Stage IV (90%).
- Skin reaction Grade 1 (50%) vs. grade 1(23.33%)) grade 2 (0%) vs. (6.67%)
- Mucosal reaction grade 1(60%) vs. grade 1(40%) grade 2(0%) vs. (10%).
- Clinical tumour response at the end of treatment complete response (6.67%) vs. complete response (0%) partial response (66.67%) vs. partial response (63.3%).
- Nodal response at the end of treatment complete response (0%) vs. complete response (0%) partial response (66.7%) vs. partial response (60%).
- Tumour status at six month of follow-up complete response (26.67%) vs. complete response (6.67%) partial response (33.3%) vs. partial response (26.67%).
- Nodal status at six month of follow-up complete response (26.67%) vs. complete response (6.67%) partial response (36.7%) vs. partial response (36.67%).
- Disease status at last follow up No disease present (26.67%) vs. No disease present (6.7%).
- Late skin toxicities grade 1(40%) vs. grade 1(36.67%).
- Late radiation mucosal toxicity (LRMT) grade 1 30% vs. 30%.
- Symptomatic relief (>50%) (26.6%) vs. (6.66%).

## DISCUSSION

The present study was carried out on sixty patients of locally advanced stage IV (A/B), histopathologically proven inoperable cases of squamous cell carcinoma of head and neck region. Patients were randomly divided in two groups of 30 patients each, patients with locally very advanced head and neck cancers were treated in group 1 with 14.8 Gy in 4 fractions over a period of 2 days with 2 fraction per day of 3.7 Gy each, 6 hours apart for 2 consecutive days and depending on the tolerance, the same schedule will be repeated for 2 more cycles each with an interval of 3 weeks. The total planned radiation dose in this group 1 were 44.4 Gy/12#/7.2 weeks. In group 2, patients treated with twice weekly palliative radiotherapy 32 Gy in 8 fractions over 4 weeks on Wednesday and Saturday.[5] Overall most patient in both group present in stage (IV) 56/60 (93.3%). Grade 1 skin reaction at 15/30 (50%) patients in Group I and 07/30 (23.33%) patients in Group II respectively. Grade 2 skin reactions were observed in 0/30 (0%) patients in group I, whereas in group II grade 2 skin reactions were observed in 2/30(6.67%) respectively.

| | Group 1 (N=30) | Group 2 (N=30) | p |
|---|---|---|---|
| Skin reaction | In Group I, 15 patients show grade 0 skin reaction and 15 patients show grade 1 skin reaction | In Group 2, 21 patient show grade 0 skin reaction and 7 patients show grade 1 skin reaction and 2 patients show grade 2 skin reaction. | 0.05 |
| Mucosal reaction | In Group I, 12 patients show grade 0 mucosal reaction and 18 patients show grade 1 mucosal reaction | In Group 2, 15 patient show grade 0 mucosal reaction and 12 patient show grade 1 mucosal reaction and 3 patients show grade 2 mucosal reaction. | 0.13 |
| Clinical tumor response at the end of treatment | (A) Complete tumor response was observed in 2 (6.67%) (B)Partial response was noted in twenty (66.67%). | Complete tumor response was observed 0 (0%) Partial response was noted in 19 (63.3%) in Group II | 0.32 |
| Nodal response at the end of treatment | (A) Nodal response at the end of treatment was complete response in 0 (0%) patients (B) Partial response was noted in 20 (66.7%) | Nodal response at the end of treatment was complete response in 0 (0%) patients Partial response was noted in 18 (60%) | 0.813 |
| Tumor status at six months of follow-up | Complete tumor response was observed in (26.67%) Partial response was noted in (33.33%) | Complete tumor response was observed in (6.67%) Partial response was noted in (26.67%) | 0.11 |
| Nodal status at six months of follow-up | Nodal response (complete response) was observed in (26.67%) Partial response was noted in (36.7%) | Nodal response (complete response) was observed in (6.67%) Partial response was noted in (36.67%) | 0.07 |
| Disease status at last follow up | No disease present in 8/30 (26.7%) | No disease present in 2/30 (6.7%) | 0.03 |
| Late skin toxicities | 12 patient show grade 1 toxicity (40%) | 11 patients show grade 1 toxicity (36.67%) | 0.79 |
| Late radiation mucosal toxicity (LRMT) | 09 patients show grade 1 and 1 patient show grade 2 toxicity. | 9 patients show grade 1 late radiation mucosal toxicity and 1 patient show grade 2 toxicity. | - |
| Symptomatic relief (>50%) | 8/30 (26.6%) patients | 2/30 (6.66%) patients | 0.03 |

Hypofractionated treatment is known to produce similar reactions in head and neck cancer patients as studies by Das. Et al.[6] and other similar studies.[7,8,9] Grade 1 mucosal reactions 18/30 (60%) patients in Group I and 12/30 (40%), patients in Group II respectively. Mucosal reactions were comparable in both the groups. Grade II mucosal reactions were observed in 0/30 (0%) and 03/30 (10%) patients in group I and group II respectively. No Grade 3 and Grade 4 mucosal reaction seen in both group. The difference in observations was statistically insignificant. Hypofractionated palliative radiotherapy is known to produce similar overall mucosal toxicity in head and neck cancer patients as reported by various authors.[10,11] Our findings are also consistent with those of Das. et al[6] and Kancherla et al.[12] Complete tumour response at the end of six months follow up in Group I and II was 08/30 (26.67%) and 02/30 (6.67%) respectively. Partial response was seen in 10/30 (33.33%) patients and 11/30 (26.67%) patients in group I and group II respectively. At end of six months, no patients developed recurrence in local disease in both group I and group II. The difference in observations was not statistically significant. Our findings are also consistent with those of Das. et al[6] and Kancherla et al.[12] At six months of follow up as per nodal response, complete nodal response was observed in 08/30

(26.67%) and 02/30 (6.67%) in group I and group II respectively. Partial response was observed in 10/30 (33.3%) in group I and 11/30 (36.67%) patients in group II. Recurrence was observed in 01/30 (03.33%) patients in group 1 and no nodal recurrence seen in group 2. There were 05/30 (17%) patients in both the groups who were N0 at the time of presentation and thus nodal response was not calculated for them. The overall results were in favour of Group I but difference in overall tumour response rates was not statistically significant Our findings are consistent with a study conducted by Kancherla et al.[12] and Das et al.[6] Overall disease status was observed at six month of follow up. No evidence disease (NED) was observed in 08/30 (26.7%) patients in Group I and 02/30 (6.67%) in Group II respectively. Symptomatic relief (Subjective regression) was observed more than 50% in 8/30 (26.6%) patients in group 1 and 2/30 (6.66%) patients in group 2. Overall symptomatic relief was better in group 1 and difference was statistically significant. Our findings are consistent with a study conducted by Soni et al.[11] and Das et al.[6] Late radiation cutaneous toxicities (LRCT) graded as per RTOG criteria observed at six months of follow up. Grade 1 LRCT noted in 12/30 (40%) cases in Group I and 11/30 (36.67%) cases in Group II. No Grade 2 and Grade 3 LRCT noted in both group. The difference in observations was not statistically insignificant. Abhishek et al. reported similar findings with respect to late radiation cutaneous toxicities as seen in our study. Late radiation mucosal toxicity (LRMT) graded as per RTOG criteria observed at six month of follow up, grade 1 LRMT noted in 09/30 (30%) cases in Group I and 09/30 (30%) cases in Group II. In both group 1/30 (3.33%) patient show Grade 2 LRMT. The difference was statistically insignificant. Our findings are consistent with similar studies conducted by Soni et al, Kancherla et al[12] and other studies in hypofractionated palliative radiotherapy in locally advanced head and neck cancer. No late radiation spinal cord morbidity and no late radiation salivary gland toxicity was detected in the patients of both the groups.

The present prospective, randomized study was carried out to evaluate the efficacy in terms of local control and toxicity of palliative radiotherapy in two different schedules in LAHNC, who were not candidates for radical treatment. This may be concluded from the present study that group 1 had better tumour control than group 2 but the difference was statistically insignificant between the two groups. Group 1 had more grade 1 skin reaction than group 2 and the difference was statistically significant. Group 1 had no grade 2 skin reaction as compare to group 2 and the difference was statistically insignificant. Grade 1 mucosal reaction was more in group 1 as compare to group 2 but the difference was statistically insignificant. Group 1 had no grade 2 mucosal reaction as compare to group 2 and the difference was statistically insignificant. Late radiation skin and mucosal reaction was comparable group in both group and the difference was statistically insignificant between the two groups. Toxicity was comparable in both groups. Overall symptomatic relief (subjective regression) was better in group 1 than group 2 and the difference was statistically significant between the two groups.

Group 1 had slightly better locoregional control, but the difference was statistically insignificant. Symptomatic relief (subjective regression) was better in group 1 than group 2.

## CONCLUSIONS

Both quad shot and twice weekly palliative radiotherapy for locally advanced head and neck cancer are comparable in term of efficacy, toxicity and feasibility.

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