

A Prospective Interventional Study to Compare Two Weeks versus Four Weeks Gap in 'Quad Shot' Regimen in Locally Advanced Head and Neck Cancers

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DOI: [10.36347/sjams.2020.v08i06.003](https://doi.org/10.36347/sjams.2020.v08i06.003)

| Received: 05.05.2020 | Accepted: 23.05.2020 | Published: 10.06.2020

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Abstract

Original Research Article

Background: Palliative radiotherapy is an effective option for incurable head and neck cancers. It is delivered by a variety of fractionation schedules. The 'QUAD SHOT' (RTOG 8502) palliative radiotherapy regimen offers an overall high palliative response in patients with locally advanced head and neck cancers. The aim of the present study was comparing the outcome of two versus four weeks gaps between consecutive cycles of radiotherapy in terms of toxicity, compliance, tolerability and loco-regional control, with reduction of overall treatment time. **Methodology:** Total 100 subjects were treated on cobalt teletherapy machine. This regimen consists of 3.7 Gy twice-daily fractions given over two consecutive days per cycle with a rest period of 2 and 4 weeks between the 3 prescribed cycles for a total dose of 44.4 Gy. Sample size is 50 cases in each group. This study was conducted at Department of Radiation Oncology, S.M.S Medical College Jaipur, and Rajasthan. **Results:** Overall palliative response is 57% in the study group while 62% in control group which is statistically non significant in both groups. Incidence of acute dermatitis and acute mucositis were higher in study group, it was statistically significant ($p=0.034$) and ($p=0.015$) respectively but manageable with supportive measures like intravenous fluid, medication and adequate nutrition. Other radiation reactions were comparable and statistically non-significant ($p>0.05$) in both treatment arms. **Conclusion:** On the basis of results it may be concluded that Two weeks gap in 'QUAD SHOT' (RTOG 8502) radiotherapy regimen can be used in locally advanced Head and Neck cancers to shorten overall treatment time without compromising overall palliation achieved in terms of symptomatic response and locoregional control with manageable toxicities.

Keywords: Palliative radiotherapy, LAHNC, Symptomatic response.

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INTRODUCTION

Head & neck cancer is the most common cancer among Indian population [1]. According to Globocan 2018 the incidence is 4.6% out of which lip and oral cavity constitute 2.0% with 3,54,864 cases, nasopharynx 0.7% with 1,29,079 cases, oropharynx 0.5% with 92,887 cases, hypopharynx 0.4% with 80,608 cases, larynx 1.0% with 1,77,422 cases, salivary glands and others 0.3% with 52,799 cases[2]. Head and neck malignancies constitute approximately 16.70% of all cancers in our department of Radiation Oncology, SMS medical college & Hospital, Jaipur Rajasthan. Tobacco, Alcohol consumption, Betel Nut Chewing, Marijuana abuse, Occupational Exposure, UV Light Exposure, Diet, Genetic Factor, and viruses and various other etiologic and risk factors are responsible for Head and Neck cancers [3-11]. Because of critical location of most of the head and neck squamous cell neoplasms, they interfere with breathing, eating and phonation, thus

affecting the quality of life. Surgery and/or chemotherapy and radiotherapy are traditionally the mainstay of the treatment of locally advanced head and neck cancers. Altered fractionation radiotherapy improves survival in patients with head and neck squamous cell carcinoma (HNSCC)[12].

In our department of Radiation Oncology, SMS medical college & Hospital, Jaipur Rajasthan most of the patients present as locoregionally advanced form (Locoregionally Advanced Head and Neck Cancer: LAHNC) requiring Concurrent Chemo-Radio-Therapy (CCRT) as the standard of care [13, 14]. However, many such patients are not suitable candidates for definitive Radiotherapy (RT). A cyclical hypofractionated palliative radiotherapy regimen, originally devised for advanced pelvic malignancies (RTOG 8502), has been successfully adapted for palliative treatment of head and neck cancers. This regimen consists of 3.7 Gy twice-daily fractions given

over two consecutive days per cycle with a rest period of 2 to 4 weeks between the 3 prescribed cycles for a total dose of 44.4 Gy. As each cycle consists of four fractions, this regimen is popularly known as the 'QUAD SHOT'. The present study will be comparing the outcome of two versus four weeks gap between consecutive cycles of radiotherapy in terms of toxicity, compliance, tolerability and loco-regional control, with reduction of overall treatment time.

MATERIAL & METHODS

This study was conducted at Department of Radiation Oncology, S.M.S Medical College Jaipur, and Rajasthan, India.

Study period

Patient recruitment was started from June 2018 to June 2019 just after getting approval of the institutional Ethical Committee.

Study universe

Locoregionally advanced head and neck cancer patients attending department of Radiation Oncology, S.M.S. Medical College & Attached Group of Hospitals, Jaipur. All patients to be included in the study were histopathologically proven.

Sample size

Sample size was calculated as per 65% rate of palliative care achieved given in seed article[8] with 95% of confidence interval, 80% power and 10% absolute error. Following above assumption, 41 cases in each arm are required as sample size for statistical analysis of present study. Therefore sample size was increased to 50 cases in each group as final sample size for present study expecting 25% dropouts/ lost to follow up/ accretion in 6 months follow up period.

Method of randomization

Patients were randomized by Chit in box method with replacement.

Assessment of toxicities

Patients were evaluated for toxicity every two weeks during radiation and thereafter during follow-up at initially monthly for three months and subsequently at three months intervals. Toxicities appearing within 90 days of the start of therapy were defined as acute toxicities. Skin reaction, mucositis, dysphagia, and xerostomia were graded according to the Radiation Therapy Oncology Group (RTOG) acute and chronic radiation morbidity criteria, whereas haematological toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Assessment of tumour response:

Symptomatic response evaluation was done during the treatment and locoregional control was evaluated after 3 months of completion of treatment

based on clinical examination and CECT/MRI of head and neck. Biopsy or fine-needle aspiration cytology was taken from any suspicious clinical and or radiological residual tumour at primary site and/or nodal area. Patients was then be categorized as per RECIST Criteria (Response Evaluation Criteria in Solid Tumours) version 1.1.

Inclusion criteria

Histopathologically confirmed malignant epithelial neoplasm of head and neck

- AJCC stage III –IV
- Patients with low performance status (PS>2) and/or not suitable for definitive treatment.
- Either sex
- Age 18-80 years
- Who gave written informed consent

Exclusion criteria

- Patients with history of prior radiotherapy to Head and Neck region
- Post operative patients
- Patients with double malignancy.
- Pregnant and lactating women.
- Patients with comorbidities.

Radiation Technique

- All patients were treated on cobalt teletherapy machine by 2-dimensional conventional radiation therapy technique.
- Patients were treated in supine position with appropriate immobilization.
- Treatment was delivered with parallel opposed/ ipsilateral field depending up on the target.
- The radiotherapy prescription was 3.7 Gy twice-daily fractions with minimum gap of 6 hours given over two consecutive days to a total of 14.8 Gy per cycle.
- Treatments were delivered for 3 cycles.
- In study group, each cycle was repeated at 2 weeks interval.
- In control group, each cycle was repeated at 4 weeks interval.

OBSERVATIONS & RESULTS

The age range of the study Population was 25-79 years and 30-80 years of the control group. In groups studied majority of patients were males (48 in the study group and 45 in control group) and rest were females (2 in the study group and 5 in control group) in table-1. In the present study, it is observed that most common site of primary tumor is oral cavity with 25 (50%) patients in the study group and 20 (40%) in the control group (Table-2). In the population studied squamous cell carcinoma was most common histology. The Most common histopathology was moderately differentiated squamous cell carcinoma (MDSCC) with 34% in the study group and 36% in the control group (Table-3). Among the population studied 26% patients were

having stage IVB and 69% were having IVA disease. The rest 5% patients were having III stage disease (Table-4). The table-5 shows symptomatic response which is objective in term of relief in pain, insomnia, trismus, placement of feeding Ryle's tube and history of weight loss. In the study group pain relieved in 72%, Insomnia 56%, Trismus 57%, reduction in placement of Ryles tube in 48% & history in weight loss in 52%. In control group pain relieved in 64% insomnia 60%,

Trismus 60% Ryle's intubation 70% and history of weight loss 56%.

Even though the symptomatic response was statistically non-significant in both the groups. The table-6 shows incidence of overall palliation achieved in both treatment groups. 57% overall palliation achieved in the study group was not statistically difference ($p=0.834$) from the 62% overall palliation achieved in the control group.

Table-1: Distribution of Cases between the Two Sexes

Sex	Study Group (50 Patients)		Control Group (50 Patients)	
	No.	%	No.	%
Male	48	96%	45	90%
Female	2	4%	5	10%

Chi-square = 0.614 with 1 degree of freedom; $p = 0.433$

Table-2: Distribution of Cases According to the Primary site of Tumor

Primary Site	Study Group (50 Patients)		Control Group (50 Patients)		Patients in both groups (100 Patients)	
	No.	%	No.	%	No.	%
Oral Cavity	25	50%	20	40%	45	45%
Oropharynx	12	24%	13	26%	25	25%
Hypo pharynx	9	18%	12	14%	21	21%
Larynx	4	8%	5	10%	9	9%
Nasopharynx	0	0%	0	0%	0	0%

Chi-square = 1.135 with 3 degrees of freedom; $p = 1.000$

Table-3: Distribution of Cases According to Histopathological differentiation

Histology	Study Group (50 Patients)		Control Group (50 Patients)	
	No.	%	No.	%
Well Differentiated Squamous Cell Carcinoma	20	40%	12	24%
Moderately Differentiated Squamous Cell Carcinoma	17	34%	18	36%
Poorly/ Un Differentiated Squamous Cell Carcinoma/malignant epithelial neoplasms	13	26%	20	40%

Chi-square = 3.513 with 2 degrees of freedom; $p = 0.173$

Table-4: Distribution of Cases According to Clinical AJCC Staging

AJCC Stage	Study Group (50 Patients)		Control Group (50 Patients)	
	No.	%	No.	%
III	1	2%	4	8%
IVA	8	16%	18	36%
IVB	41	82%	28	56%

Chi-square = 8.095 with 2 degrees of freedom; $p = 0.017$

Table-5: Symptomatic Response

Presenting symptoms prior to QUAD SHOT (RTOG 8502)	Study Group (41 Patients)				Control Group (46 Patients)			
	n	%	Palliative Response		n	%	Palliative Response	
			# of Responders	% of Responders			# of Responders	% of Responders
Pain	35	87%	25	72%	40	85%	26	64%
Insomnia	36	88%	21	56%	36	90%	22	60%
Trismus	4	9%	2	57%	5	8%	3	60%
Ryle's Tube feeding	3	5%	1	48%	4	7%	3	70%
Weight loss	5	11%	3	52%	14	30%	8	56%

Chi-square = 0.037 with 1 degree of freedom; $p = 0.512$, NS

Table-6: Overall Palliation Achieved

Overall Palliation Achieved	Study Group (41 Patients)		Control Group (46 Patients)	
	No.	%	No.	%
Yes	24	57%	29	62%
No	17	43%	17	48%

Chi-square = 0.044 with 1 degree of freedom; $p = 0.834$, NS

DISCUSSION

Palliative radiotherapy is an effective option for incurable Head and neck cancers is delivered by a variety of fractionation schedules. The 'QUAD SHOT' (RTOG 8502) palliative radiotherapy (RT) regimen offers an overall high palliative response in patients with locally advanced Head and Neck cancers who are not suitable for curative treatment with limited life expectancy.

Symptomatic response was subjective relief of symptoms like pain, insomnia, trismus, requirement of feeding tube placement and history of weight loss. The clinical response rates (LRC = locoregional control) obtained after 6 months of treatment follow up reveals that complete response (CR) was achieved in 1 patient (2%) in the control group and none in the study group. The partial response (PR) rates were 28 patients (69%) in the study group and 23 patients (72%) in the control group. Overall response rates (CR+PR) was 69% in study group and 74% in the control group and was statistically non-significant ($p=0.634$). 57% (24 patients) had an overall palliative response in the study group while 62% (29 patients) in the control group which is statistically non significant in both groups ($p=0.834$). The overall palliative response achieved in both groups in our study is comparable to achieved by Corry *et al.* [15]. The study consisted of 14 Gy in four fractions, given twice a day and at least 6 hours apart, for 2 consecutive days. The regimen was repeated at 4 weekly intervals for a further two courses i.e. upto 42 Gy in 12 fractions, if there was no tumour progression. The aims of the study were to evaluate the rate of tumor response (primary) and toxicity, quality of life (QoL) and survival in such patients (secondary). Both compliance rate to all the three cycles and objective response rate was 53.3%. Median overall survival was 5.7 months, median progression free survival was 3.1 months. Improvement in QoL was noted in 44% of the patients. Chen *et al.* [16] reviewed the University of California Davis School of Medicine experience in 60 patients who underwent a variety of hypo fractionated palliative regimens for recurrent or incurable head and neck cancers including the RTOG 8502, 70 Gy in 35 fractions, 30 Gy in 10 fractions, 37.5 Gy in 15 fractions, and 20 Gy in 5 fractions. The results were generally superior to the other fractionation schedules reviewed which reported palliative response ranging from 60 – 86%. Lok *et al.*[17] have reported that 37% of their patients completed at least three cycles while 65% had a palliative response. Median overall survival was 5.67

months. On survival analysis, palliative response ($p < 0.001$), KPS ≥ 70 ($P = 0.001$), and greater number of cycles ($p = 0.02$) remained independent predictors of improved survival. Das, *et al.* [18] treated 36 LASCCHN cancer patients with 40 Gy in 10 fractions with 2 fractions per week. Compliance rate was 73% and the median overall survival of the cohort was 7 months. The "Hypo Trial" conducted by Porceddu and Colleagues[19] treated 35 incurable head and neck cancer patients with the goal of 30 Gy in 5 fractions with 2 fractions per week. Thirty-one (88%) of the patients received at least 30 Gy. Overall 80% of patients experienced an overall objective response.

Mudgal *et al.* [20] observed good objective response in 82.6% and 84.7% of patients at primary and nodal sites, respectively. Jakhar *et al.* [21] performed a pilot study to evaluate the effect of an accelerated hypofractionated 4 days schedule (octa shot) in providing palliation to such advanced cases of head and neck cancer. After completion of radiotherapy, first response evaluation done at 15th day showed $\geq 50\%$ objective response in 14 patients. At 1 month, this response increased to $\geq 75\%$ in 16 patients and 50%–75% in three patients. None of the patients had disease progression. Improvement in symptoms was reported with respect to pain and dysphagia by patients subjectively. The overall palliative response rates achieved in our study was comparable to above mentioned various standard hypofractionated palliative regimen.

CONCLUSION

We conclude that Two weeks gap in 'QUAD SHOT' (RTOG 8502) radiotherapy regimen can be used in locally advanced Head and Neck cancers to shorten overall treatment time without compromising overall palliation achieved in terms of symptomatic response and locoregional control (LRC) with manageable toxicities. Larger prospective randomized studies with longer duration of follow up may be needed for strong evaluation of efficacy, toxicity profile and to draw inference on locoregional control (LRC), Disease Free Survival (DFS), median survival and overall survival (OS).

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