



PALLIATIVE RADIOTHERAPY IN HEAD AND NECK CANCERS – LOOKING BEYOND 30GY, A COMPARATIVE STUDY OF TWO FRACTIONATION SCHEMES.

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ABSTRACT

The rising incidence of head and neck cancer is a significant problem in our country as majority of them present as locally advanced disease. In spite of many clinical trials in this field hypofractionated radiotherapy remains less studied and needs more research. Objective- Assess the acute toxicities, objective response, subjective response, Progression free survival and Overall survival in both treatment arms. Methods and materials- This is a comparative prospective randomized controlled unblinded study with two arms, 60 patients with inoperable locally advanced head and neck cancers were enrolled in the study. 30 patients in each arm from September 2017 to September 2019. Arm A received 30Gray in 10 fractions and Arm B received 25Gray in 4 fractions over two weeks period. Toxicities and symptomatic relief during treatment was noted. Radiological response was assessed every four weeks up to three months. Survival was followed up to six months. Results- Grade 3 oral mucositis was seen in both arms. Other toxicities were grade 1 dermatitis, grade 2 pharyngitis and laryngitis in both Arms. Pain, dysphagia, dyspnea and trismus improved in both arms after completion of radiotherapy. Objective response was similar in both arms. PFS and OS at 6 months were better in Arm B than in Arm A. Conclusion- Biweekly palliative radiation schedule was convenient and avoided long hospital stay for the patients and their relatives who came from far away rural areas.

KEYWORDS : Palliative Radiotherapy, Head And Neck Cancers, Hypofractionation, Palliation.

INTRODUCTION

Head and neck cancer constitute approximately one third of all cancer cases in India in contrast to 4% to 5% in the developed world. Majority of head and neck cancers in India present as locally advanced disease. In most cases, due to extensive locoregional involvement, poor general condition of the patient, or comorbid conditions curative treatment is not an option. In spite of many trials in the management of head and neck cancers, palliative radiotherapy remains less studied and needs more research. Our study is a comparative study based on palliative radiotherapy in inoperable locally advanced head and neck cancers.

MATERIALS AND METHODS

This study was carried out to compare the acute toxicities, response to treatment, progression free survival and overall survival associated between the two arms of hypofractionation. The period of study was from September 2017 to September 2019 including follow up. Patients with histologically proven squamous cell carcinoma of locally advanced inoperable head and neck cancers (TNM Staging T4B, any N, M 0) aged between 18 to 70 years with ECOG 2 and 3 with written informed consent in patient's own language were included in the study. Patients with orocutaneous fistula and those who received radiotherapy previously for same disease were excluded. With block randomization all 60 patients were randomized between the two study arms with 30 patients in each arm. Pretreatment evaluation of all patients included complete hemogram, biochemical profile, complete ENT examination, CECT Head and neck (target lesions defined using RECIST criteria), Xray chest and USG of abdomen pelvis. Patients were treated on Theratron 780E (Cobalt 60). The treatment volume included the symptomatic gross primary tumor and or the gross nodal disease. ARM A received a total dose of 25Gy in 4 fractions, 6.25Gy dose per fraction, 2 fractions per week for two consecutive weeks (each fraction 3 days apart). ARM B received a total dose of 30Gy in 10 fractions in two weeks. All patients were evaluated for toxicity once a week during treatment (maximum grade of acute toxicity with RTOG/EORTC criteria) and supportive care was given when indicated. Response evaluation was done on weeks 4, 8 and 12 after completion of radiotherapy. On every

visit the patients were evaluated for grade of trismus (maximal inter incisor mouth opening), dysphagia (dysphagia score) and dyspnea (medical research council dyspnea scale). Pain was assessed according to Numerical Pain Rating Scale. All clinical analysis was done according to RTOG criteria. Continuous variables were presented as median +/- SD (standard deviation) and compared between two arms by performing unpaired t-test. Categorical variables were expressed in actual numbers and percentages and compared using the Student t-test. All the test were two sided. P Value <0.05 was considered statistically significant. Statistical software Epi Info, Open Epi and Microsoft Excel was used for statistical analysis.

RESULTS

The patient characteristics are expressed in *Table 1*. Most common presenting age group was 45-65 years. Pain was the most common presenting symptom seen in all the patients. **Toxicity assessment**= During the first week of radiation Grade I Mucositis (1 patient in each arm), Grade I Pharyngitis (ARM A- 2 patients, ARM B- 1 patient) and Grade I laryngitis (ARM A- 2 patients, ARM B- 1 patients) was seen in both arms. During the second week of radiation Grade I Dermatitis (ARM A- 3 patients, ARM B- 10 patients P value- 0.02), Grade III mucositis (ARM A-2 patients, ARM B- 1 patient), Grade II pharyngitis (ARM A-14 patients, ARM B- 15 patients) and Grade II laryngitis (9 patients in each arm) was seen. **Subjective response assessment**= Assessment was done on weeks 4, 8, 12 after radiation. The response was nearly similar in both the arms and there was improvement of all the signs and symptoms. **Objective response assessment with RECIST CRITERIA**= At 12 weeks after radiation Complete Response was seen in 0 patient in ARM A and 1 patient in ARM B. Partial response was seen in 15 patients in ARM A and 13 patients in ARM B *Table 2*. **Survival at 6 months** = In ARM A the PFS (Progression free Survival) was 36.66% and OS (Overall Survival) was 70% whereas in ARM B the PFS was 16.66% and OS was 46.66%.

DISCUSSION

The reason why majority of the patients of head and neck cancers in India present in the locally advanced inoperable

stage is that there is lack of knowledge and awareness about cancer and its symptoms and the inability to accurately diagnose the cancer thus failing in providing accurate treatment. Apart from these the patients prefer to take over the counter drugs for symptomatic relief neglecting their disease and only visit a specialist after the symptoms get worse.

They also fear undergoing major surgeries. All of these leading them to trust in alternative forms of medicine. When these patients reach a radiotherapy institute for treatment their primary objective is relief from the longstanding symptoms. The bulky disease, pain, bleeding, hoarseness, dysphagia and dyspnea is unbearable in stage IVB for majority of the patients. The rationale of using hypofractionated radiotherapy in this group of patients is that it helps in palliating the symptoms in a shorter time period. In our study the subjects in ARM B received 30Gy in 10 fractions.

The Biological Effective Dose (BED) for tumor cells with α/β ratio of 10 is 39Gy with an EQD2 (equivalent dose at 2Gy/fraction) of 32.5Gy. The BED for the spinal cord (α/β ratio 2) is 75Gy with an EQD2 of 37.5Gy. Caution was taken to spare the spinal cord as much as possible from radiation. The subjects in ARM A received 25Gy in 4 fractions. The BED for tumor cells with α/β ratio of 10 is 40.63Gy with an EQD2 of 33.85Gy. The BED for spinal cord in ARM B with α/β of 2 was 103Gy with an EQD2 of 51.56Gy. Considering the tolerance dose for spinal cord to be 45Gy, it was essential to spare the spinal cord as much as possible. With lesser number of fraction we completed treatment before accelerated repopulation of tumor cells. The high per fraction dose of 6.25Gy is lethal for the dividing tumor cells and gives maximum response from the slow responding and dormant tumor cells (as they can repair the sub lethal damage). Hence using hypofractionation is a better way to tackle these cells.

H Cocks et.al have quoted that- Hypofractionated or short course radiotherapy should be considered for local pain control and for painful bony metastases.

In the QUAD SHOT regimen 14Gy delivered in four fractions, given twice a day, at least 6hrs apart, for 2 consecutive days. This regimen was repeated at 4 weekly intervals for two more courses if there was no tumor progression. 30 patients (29 Stage IV, 20 ECOG 2-3) had at least 1 treatment and 16 patients completed all three cycles. Sixteen patients (53%) had an objective response (2CR, 14PR) and 7 had stable disease. Median OS was 5.7 months, median PFS was 3.1 months.

The treatment was very well tolerated. QUAD SHOT regimen is effective for palliation with minimal toxicity and a good response. Spartacus R.K et.al. conducted a retrospective study with 98 patients of stage IV head and neck cancers. Patients treated with palliative radiotherapy 25Gy in 4 fractions, 1 fraction (6.25Gy) per week. The primary end point was relief of symptoms and treatment response in the 4th week after radiotherapy. Acute toxicity was graded as per the RTOG criteria.

All patients had >50% pain relief. Dysphagia was improved in 82% of patients. Dyspnea improved in all the symptomatic patients. Tumor complete response (CR) was seen in 2 patients, partial response in 89, stable disease in 3, and progressive disease in 4. Grade II and III acute skin and mucosal toxicities were seen in 29% and 27% cases, respectively. Murthy V et.al. studied the efficacy of a twice-weekly hypofractionated palliative radiotherapy schedule in locally very advanced head and neck cancers. 126 patients were enrolled in the study. 93 (73.8%) patients who completed the planned treatment of 32Gy in 8 fractions were included in the symptom analysis. Overall response rates were 42% at

primary disease and 55% at nodal disease. 76.3% of the patients reported pain relief ($P = 0.001$) and 42.8% patients reported improvement in anxiety and depression ($P = 0.001$). The median survival of the patients was 5.5 months. Acute grade III mucositis was seen in one patient (1.2%). The radiotherapy regimen was effective for sustained symptom palliation with low acute toxicity in locally very advanced head and neck cancers.

Michael Laursen et.al. conducted a retrospective study of outcomes in patients of hypofractionated radiotherapy with a palliative intent in head and neck cancers. 77 newly diagnosed head and neck cancer patients were planned for 52–56Gy in 13–14 fractions twice weekly. 75% patients completed the treatment. Locoregional tumor response at 2 months was 45%. Grade III or IV acute mucositis were observed in 25%, and grade III or IV acute dermatitis observed in 15% patients.

This study concluded that palliative hypofractionated radiotherapy with 52–56Gy in 13–14 fractions had good tumor response and tolerance in a vulnerable patient population. However, it may not be suited for patients in poor performance status.

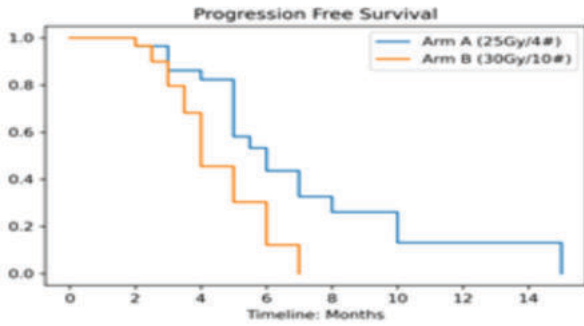
In our study the BED for normal tissue long term toxicity in ARM A was 181Gy. But since the survival of the patients was not long enough to face the late toxicities, this high BED was not a matter of concern. Acceptable symptomatic palliation was achieved in majority of the patients in both arms. This study also proves the effectiveness of hypofractionation in patients with a PS of 2 and 3. In an institute that deals with a large number of cancer patients yearly this hypofractionated radiotherapy schedule can optimize available resources in terms of technical workforce and machine time. The bi-weekly schedule was convenient to the patient who had to travel for treatment only twice a week.

Table 1

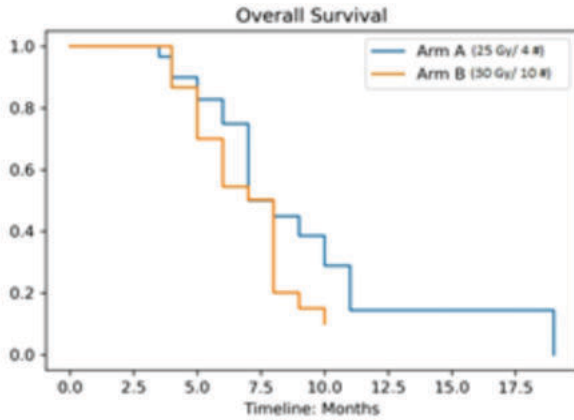
Characteristics	Arm A (%)	Arm B (%)
Age group in years		
• <35	00 (0.0)	01 (1.6)
• 35-45	04 (6.6)	07 (11.6)
• 45-55	11 (18.3)	06 (10.0)
• 55-65	09 (15.0)	08 (13.3)
• >65	06 (10.0)	08 (13.3)
Sex Determination		
• Male	21 (35.0)	17 (28.3)
• Female	09 (15.0)	13 (21.6)
Performance status (ECOG)		
• 2	26 (43.3)	21 (35.0)
• 3	04 (6.6)	09 (6.6)
Involved primary site		
• Buccal mucosa	15 (24.9)	11 (18.2)
• Supraglottis	07 (11.6)	02 (3.3)
• Base of tongue	01 (1.6)	03 (5.0)
• Tongue	02 (3.2)	04 (6.6)
• Others	05 (8.3)	10 (16.6)
Presenting sign & symptom		
• Pain (NRS) mean	6.56	6.46
• Dysphagia	28 (46.6)	26 (43.3)
• Trismus	20 (33.3)	15 (25.0)
• Dyspnea	08 (13.3)	04 (6.6)

Table 2

Response at 12 weeks	ARM A	ARM B	P value
• Partial response (PR)	15	13	0.60
• Complete response (CR)	00	01	0.31
• Progressive disease (PD)	10	10	0.38
• Stable disease (SD)	06	06	0.54



Graph 1



Graph 2

CONCLUSION

The biweekly hypofractionated radiotherapy regimen of 25Gy in 4 fractions is equally effective in palliation like the 30Gy in 10 fraction regimen. In fact, it is time conserving and more feasible for the patient. It is necessary that more research is done on these regimens of hypofractionation to save resources and provide necessary treatment at the same time to our needy patients of India.

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