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A PROSPECTIVE RANDOMISED COMPARATIVE STUDY OF TWO PALLIATIVE RADIOTHERAPY REGIMENS IN ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK REGION

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ABSTRACT This single-institutional prospective study was initiated to compare two common Palliative Radiotherapy regimes in terms of symptom relief and disease control with acceptable toxicities. 64 patients were recruited for the study after institutional ethical committee clearance and informed consent. Patients were divided into ARM A (External Beam Radiotherapy 30Gy in 10 fractions over 2 weeks) and ARM B (EBRT 20Gy in 5 fractions over 1 week). 61 patients 31 in ARM A and 30 in ARM B were evaluable for analysis. The two groups were comparable in terms of age and sex distribution, performance status, stage, primary site and histological grade. Results showed that both the Hypofractionated Radiotherapy regimens are equally effective palliative tools for controlling symptomatic disease in patients with advanced head and neck cancers with acceptable toxicities. The shorter Palliative regimen of 20 Gray in 5 fractions is an acceptable alternative in resource constrained Department like ours.

KEYWORDS : Palliative Radiotherapy, Hypofractionated Radiotherapy, Locally Advanced Head Neck Cancer

Cancers of head neck region (excluding brain tumours) is the third most common malignancy seen in both sexes across the globe[1-7] and is the commonest malignancy in males all over India[1,5]. Around 60% of the patients present with loco-regionally advanced stage[2,4,6]. Palliative Radiotherapy is the mainstay of treatment in locally Advanced Head and Neck Cancers due to their advanced disease and often poor performance status. In India, cancers of oral cavity, tongue, pharynx and larynx contribute a major share. Head Neck cancers are strongly correlated with smoking[8,9] and tobacco chewing[10,11] habits and also excessive alcohol consumption over long duration[12,13]. For the past 25 years there has been an increasing trend of oropharyngeal cancer due to Human papilloma virus -16 infection[14,16].

Most of the patients present in our out-patient department in a very advanced stage[17,18] and are treated by Palliative Radiotherapy[17]. Symptomatic relief and tumour regression in a short interval of time without major acute toxicity[18,19] is the aim.

Two common Palliative Radiotherapy schedules -30 Gray in 10 fractions and 20 Gray in 5 fractions are almost equally effective in tumour regression, acute toxicity profile and symptom relief[19].Considering the huge burden of patients and lack of resources, shorter fractionation regime of 20 Gray in 5 fractions is an attractive palliation option in our set up .

MATERIALS AND METHODS

The prospective randomised study was conducted in the Department of Radiotherapy, Burdwan Medical College Hospital, Bardhaman, West Bengal. Patients attending the Radiotherapy Out-Patient Department (OPD) from January 2018 to July 2019 with biopsy proven advanced squamous cell carcinoma of head neck region with ECOG performance status 0-3 and planned for Palliative Radiotherapy were included. Patients with prior Radiotherapy, Chemotherapy and severe co-morbid conditions were excluded.

Local and regional control was assessed by clinical examination and standard investigation procedures. Acute Toxicity was assessed by RTOG common toxicity criteria for Adverse events. Time to recurrence of Tumour and reappearance of symptoms as per patient's statement was recorded using One Rupee Scale.

Primary objective of the study was to compare Loco-regional control, Palliation of symptoms and Acute toxicity profile in the two common Palliative Hypofractionated Radiotherapy regimes.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS version 20. For categorical variables, Chi Square and Fisher Exact tests were used, while for continuous variables, the mean and SD were compared using Independent samples t test with 95% CI. All tests were 2-tailed and p value less than 0.05 was taken.

RESULTS AND ANALYSIS

After clearance from Institutional Ethics Committee, 64 patients were assessed for eligibility for the study. 61 patients were evaluable. 31 patients were allotted into Arm A (30 Gray in 10 fractions over 2 weeks) and 30 patients into Arm B (Study arm- 20 Gray in 5 fractions over 1 week) after fulfilling the eligibility criteria and taking proper informed consent. Both the groups were comparable in terms of age distribution, sex stage, primary site and histological grade.

Table No 1: Patient profile

	Arm A (n=31)	Arm B (n=30)	P value
Sex			
Male	27(87.09%)	26 (86.67%)	0.9603, not significant
Female	4 (12.9%)	4 (13.33%)	
Age			
40-49 yrs	2 (6.45%)	3 (10.00%)	0.7788, not significant
50-59 yrs	11 (35.48%)	12 (40%)	
60-69 yrs	18 (58.06%)	15 (50.00%)	
ECOG Performance status			
ECOG 1	16 (22.58%)	12 (23.33%)	0.648, not significant
ECOG 2	13 (35.48%)	16 (40.00%)	
ECOG 3	2 (41.94%)	2 (36.67%)	
Primary Site			
Oral cavity	11 (35.48%)	10 (32.25%)	0.9971, not significant
Oropharynx	8 (25.80%)	9(30.00%)	
Hypopharynx	3 (9.68%)	3 (10.00%)	
Larynx	8 (25.58%)	7 (23.33%)	
Nasopharynx	1 (3.22%)	1 (3.33%)	
AJCC Stage			
III	1 (3.22%)	2 (6.67%)	0.6699, not significant
IV A	13 (41.93%)	16 (53.33%)	
IV B	16 (51.61%)	11 (36.67%)	
IV C	1 (3.22%)	1 (3.33%)	
Histological Grade			
Well differentiated	5 (16.31%)	12 (40.00%)	0.0872, not significant
Moderately differentiated	16 (51.61%)	9 (30.00%)	
Poorly differentiated	10 (32.25%)	9 (30.00%)	

RESPONSE EVALUATION

Patients were evaluated 6 weeks following completion of treatment for response which was evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST criteria version 1.1). In the ARM A, 1 patient (3.22%) achieved Complete Response (CR) while 1 patient (3.33%) achieved CR in the ARM B which is of no statistical significance. In the ARM A, 18 patients (58.06%) achieved Partial Response (PR) while 16 patients (53.33%) achieved Partial Response. 19 patients (61.29%) achieved overall response (CR+PR) in ARM A while it was 17 in the ARM B (56.66%) which is not statistically significant. Pain control was scored by questionnaire method and using one Rupee scale and there was no statistical difference between the two arms. Acute Toxicities like mucositis, skin toxicity and xerostomia were studied according to CTCAVEv3 and were comparable.

Table 2: Treatment Outcome

	ARM A (n=31)	ARM B (n=30)	p-value
CLINICAL RESPONSE			
Complete P-value (CR)	1 (3.22%)	1 (3.33%)	
Partial Response (PR)	18 (58.06%)	16 (53.33%)	
Stable Disease (SD)	7 (22.58%)	7 (23.33%)	
Overall response (CR+PR)	19 (61.29%)	17 (56.66%)	0.9788, not significant
PAIN CONTROL			
Mild	3 (9.67%)	2 (6.45%)	
Moderate	11 (35.48%)	8 (26.66%)	
Significant	17 (54.83%)	20 (66.67%)	
Overall Palliation	28 (90.32%)	28 (93.33%)	0.6374, not significant
TOXICITY- Acute			
SKIN as per CTCAEv3			
Grade 1	15 (48.38%)	10 (33.33%)	
Grade 2	10 (32.26%)	11 (36.67%)	
Grade 3	5 (16.12%)	7 (23.33%)	
Grade 4	1 (3.22%)	2 (6.66%)	
Overall Grade 2 or more	16(51.60%)	20 (66.66%)	0.6373, not significant
MUCOSITIS as per CTCAEv3			
Grade 1	11 (35.48%)	8 (26.66%)	
Grade 2	12 (38.71%)	11 (36.67%)	
Grade 3	7 (22.58%)	9 (30%)	
Grade 4	1 (3.22%)	2 (6.66%)	
Overall Grade 2 or more	20 (64.52%)	22 (73.33%)	0.7808, not significant
XEROSTOMIA			
Grade 0	2 (6.45%)	1 (3.33%)	
Grade 1	12 (38.07%)	9 (30.00%)	
Grade 2	15 (48.38%)	16 (51.61%)	
Grade 3	2 (6.45%)	4 (13.33%)	
Grade 2 or more	17 (54.83%)	20 (66.67%)	0.6951, not significant
MORBIDITY			
DYSPHAGIA -TUBE FEEDING	9 (29.03%)	6 (20.00%)	0.4128, not significant
HOSPITAL ADMISSION	7 (22.58%)	5 (16.66%)	0.5613, not significant
TOXICITY 3 months >/= Grade 3			
SKIN	4 (12.90%)	5 (16.67%)	0.6786, not significant
ORAL MUCOSA	7 (22.58%)	7 (23.33%)	0.9443, not significant

Follow-up at 3,6,9 and 12 months did not show any statistically significant difference in progression free survival between the two arms.

DISCUSSION

Squamous cell carcinoma of head and neck constitutes about 30-40% of all cancer in India. Majority presents in advanced stage. Radiotherapy is the commonest single treatment for patients with unresectable and/or inoperable locally advanced head and neck cancers. Historically, patients with unresectable HNSCC treated by RT alone had locoregional control rates between 50 and 70% and 5-year survival rates of 10-20%. Radio-biologically, shorter overall treatment time leads to increased tumour cell kill and improved results in head and neck cancer patients[20,21,22]. In these patients with short survival, rapid symptom relief within a short time is the aim.

The present study was conducted to evaluate whether shorter 20 Gray in 5 fractions over 1 week gave comparable disease palliation to 30 Gray in 10 fractions over 2 weeks in Locally Advanced Head Neck Cancer with acceptable toxicities.

Weissberg et al. compared conventionally fractionated 60 to 70Gray in 6-7 weeks versus hypofractionated (40Gray to 48 Gray in 10 to 12 fractions at 400CGy/fraction) palliative external beam radiotherapy schedules in 64 patients with stage III-IV unresectable head neck squamous cell carcinoma. No differences were noted in tumour control, acute side effects or long term sequelae[23].

The "Hypo Trial" planned 37 patients to receive 30 Gray in 5 fractions at 2 fraction/week, at least 3 days apart, with an additional boost of 6 Gray for small volume disease (≤ 3 cm) in suitable patients. 31 (88%) received >30 Gray. The overall objective response was 80% grade3 mucositis and dysphagia were experienced in 26% (9/35) and 11% (4/35) respectively. 13(62%) reported an overall improvement in quality of life and 14 (67%) experienced in improvement of pain[17].

The QUAD SHOT regime gave 14 Gray in 4 fractions given 2 fractions each day over 2 days with fraction gap at least 6 hours apart. This was repeated at 4 weekly intervals for further 2 courses if there was no tumour progression.30 eligible patients (29 stage IV, 20 performance status 2-3) had at least one treatment and 16 (53%) patients completed all three cycles. 16 patients had an objective response, 2 Complete Response, 14 Partial Response and further 7 had Stable disease. The treatment was well tolerated with improved quality of life in 44%[24].

Vikram suggested that the advanced head and neck cancers from developing countries don't show favourable outcome. 808 untreated head and neck cancer patients (91% stage IV) were followed up longitudinally, the median survival time was approximately 100 days. When the patient has 80% of likelihood of death within 12 months due to advanced disease, palliative treatment is the standard therapeutic decision[25].

Ghoshal et al. studied 25 patients with stage III and IV head and neck cancer who were treated with a short course palliative radiotherapy 30 Gray in 10 fractions over 2 weeks, primary end point showed relief of symptoms in the 4th week after radiotherapy. All 22 patients with pain and 90% of patients with dysphagia, dyspnoea and >50% patients had improvement of disturbed sleep after radiotherapy. Cough was relieved in 60% of cases[26].

Mohanty et al. studied 505 patients with stage IV head and neck squamous cell carcinoma using regime of 20 Gray/5 fractions once daily over 1 week. At 1 month 189 patients (37%) achieved a Partial Response and had ambulatory physical state suited for further curative dose of radiotherapy. Most of them reported good symptom control (>50%for pain,53% for dysphagia, 57% for hoarseness, 47% for otalgia 76% for respiratory distress and 59% for cough the main acute toxicity was patchy oropharyngeal mucositis and dermatitis[4].

Talapatra et al. in an extensive review favoured a short course fractionated regime (20 Gray/5 fractions or 30 Gray in 10 fractions over cyclical treatment (QUAD SHOT) over protracted courses of radiotherapy for the purpose of palliation[18].

The majority of patients in both the groups in our study experienced comparable symptomatic and objective tumour response (CR and PR) with acceptable toxicity similar to other studies.

The limitation of our study was standardized quality of life evaluation was not under taken and thus, quantification of improvement of quality of life was not possible. This is a common problem and similar to other studies reporting outcomes of palliative RT for patients with Head and neck cancer[4,19,27,28].

The major limitations of this study were small sample size and short

follow-up period.

SUMMARY AND CONCLUSION

Head Neck cancers are the commonest non haematologic cancers in India. Most are Locally advanced and Palliative Hypofractionated Radiotherapy is the standard treatment offered. 30 Gray in 10 fractions and 20 Gray in 5 fractions are the commonest schedules used. The present study showed that the results of the two regimes are comparable in terms of symptom relief, disease control with acceptable toxicities. Shorter regime of 20 Gray in 5 fractions is an acceptable alternative and is particularly attractive in resource constrained heavy burdened set up like ours.

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