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Incurable head and neck cancers: Will quad shot be an optimum shot?

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ABSTRACT

Objective: The primary objective was to estimate palliation of symptoms and tumour response. The secondary objective was to evaluate the toxicity and outcome in three palliative hypo fractionated regimens. i.e. conventional, Quad shot schedule, Quad shot with concurrent chemotherapy.

Methods: The patients were randomly divided into 3 arms. Arm1 received conventional schedule -30 Gy in 10 fractions, one fraction per day for a period of 2 weeks; Arm 2 patients received quad shot schedule - 14.4 Gy in 4 fractions, 2fractions per day, 6 hours apart, a total of 2 sessions; Arm 3 patients received quad shot schedule-14.4 Gy in 4 fractions, 1 fraction per day with chemotherapy-Carboplatin (AUC2) on day 1 of each cycle, total of 2 sessions. patients were assessed 4 weeks post 1 session, those with progressive disease or grade 3/4 toxicity patients were managed with best supportive care. Patients were evaluated for palliation of symptoms post-phase 1, post phase 2, followed by at 1month, 2months up to 6 months' after completion of phase 2 radiation.

Results: The pain relief in arm1, arm 2, arm 3 was 72% (39/55), 82.6% (43/53), and 79.2% (41/52) respectively. Improvements in dysphagia in arm1, arm2, arm3 were 64.2% (35/55), 75% (40/53), and 75% (39/52) respectively. The Grade 2 mucositis were 36% (18/55), 20.7% (11/53), 23.07% (12/52) and grade 3 mucositis were 29% (11/55), 7.54(4/53), 9.6% (5/52) in arm 1, arm 2, arm 3 respectively. The number of patients with grade 1 dermatitis were 36.67% (20), 20% (11), 23.33% (12) and 13.3% (7), 3.33% (2) and 3.33 (2) in arm1, arm 2, arm 3 respectively. Partial response was observed in 25.45% (14/55), 36.67%, (19/53) and 33.33% (17/52) in arm1, arm 2 and arm 3 and stable disease was 56.67% (31/55), 53.33% (28/53) and 56.67% (30/52) respectively. QoL improved in all three arms.

Conclusion: Quad shot regimen with or without chemotherapy is comparable with conventional palliative schedule and is associated with adequate symptom relief with acceptable toxicity and better compliance.

Key words: palliation, radiotherapy, quad shot, head and neck cancer, carboplatin

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INTRODUCTION

Globally, Head and Neck Squamous Cell Carcinoma (HNSCC) is the seventh most common cancer, resulting in about 300,000 deaths per year [1]. According to national cancer registry (India) the incidence of head and neck cancer is 52.22% in oral cavity, 19.16% in Oropharynx, 12.83% in Hypopharynx, 12.87% in larynx and 2.89% in nasopharynx. The proportion of head and neck cancer in India presenting with localized disease is 25.2%, loco-regional disease is 66.6%, distant metastasis is 4.8% and unknown extent is 3.4%. The majority of patients presenting with loco-regional advanced disease at diagnosis are not suitable for curative treatment due to poor performance status and associated co-morbidities [2, 3]. Although Patients with advanced HNSCC without curative treatment have limited oncological outcome and shortened survival rate but deserve some sort of therapy to mitigate local symptoms like pain, bleeding, dysphagia, and loco-regional disease [4-8].

Palliative Radiotherapy (PRT) is one of the modalities to palliate the local symptoms from locally advanced Head and Neck Cancer (HNC) [9]. The optimum radiation dose and fractionation schedules are not standardized due to lack of evidence from randomized controlled studies. The main objective of any palliative RT course should be to achieve significant symptom control, minimum side effects, adequate tumour regression, with shorter treatment time and yet preserving the quality of life [10, 11].

This study in high volume centres is intended to assess the outcomes of different palliative RT schedules for incurable HNC and impact over disease control, alleviation of troublesome symptoms and on Quality of Life (QOL).

MATERIALS AND METHODS

After obtaining institutional review and ethical board clearance, one hundred sixty-four (164) histologically proven, locally advanced head neck cancer patients were randomized in to three arms. The randomization was done by computer generated randomization table. The standard arm was Arm 1, in which patients received palliative radiation dose schedule of 30Gy in 10 fractions, delivered 5 fractions per week over two weeks. The arm2 and arm 3 were experimental arms where arm 2 received radiation QUAD shot schedule of 14.4Gy in 4 fractions, delivered twice a day 6 hours apart for 2 days and the same schedule was repeated after 4 weeks. The patients in arm 3 received concurrent

carboplatin along with modified QUAD shot radiation regimen where radiation dose of 14.4Gy in 4 fractions was delivered once daily for 4 days.

Radiotherapy and chemotherapy details

The informed consent was obtained from all the eligible patients. A detailed clinical, medical, past and family history was obtained. A thorough clinical examination including DL scope was done for all patients along with basic hematological investigations like complete hemogram, liver and renal function test. As a part of staging and metastatic work-up, contrast enhanced Computed Tomography (CECT) of head, neck and thorax was done and staged according to AJCC TNM staging 8th edition.

Radiotherapy details

Eligible patients were immobilized using thermoplastic head and neck cast in supine, hands by the side and neck in suitable position. Intravenous contrast enhanced simulation CT scan was acquired from vertex to sternal angle at 5 mm slice thickness. The acquired images were sent to contouring workstation. The gross tumor volumes (GTV primary and nodal) and organ at risk contoured and planning was done by field in field (fif) 3 dimensional conformal techniques (fif 3DCRT). The aim of plan was to achieve 95% of the volume to receive 95% of dose (V95 to 95%). The maximum dose (D max) was aimed to be less than 107% preferably inside GTVs.

Dose prescription

The patients randomized to arm1 were treated to a total dose of 30Gy in 10 fractions (30Gy/10#), five fractions per week for two weeks. The arm 2 patients received QUAD shot radiotherapy regimen in which a total radiation dose 14.4Gy was delivered in four fractions (14.4Gy/4#), two fractions per day, 6 hours apart for two days. The same schedule was repeated after 4 weeks if at least partial response or more recorded and not associated with Grade 3 or grade 4 toxicities. The patients in third arm were treated with modified QUAD shot in which 14.4Gy in 4 fractions delivered once day over 4 days along with concurrent carboplatin (AUC2) on the first day. The same schedule was repeated after 4 weeks for patients having at least partial response. In phase 2, target volumes were adapted according to the response observed in re-simulation scans.

Response Assesment, toxicity and scoring

Prior to the start of radiation, baseline disease burden (both primary and nodal) and symptoms were recorded. Quality of life assessment was done and recorded using validated questionnaire of EORTC QLQ H&N 35. The objective tumour response was assessed according to RECIST 1.1 criteria using CECT 4 weeks after the completion of phase 1, and 4 weeks after completion of phase2. The subjective response and palliation of symptoms were assessed at the time of objective response. The hematological, mucosal and dermal toxicities were scored using RTOG grading criteria.

Statistical analysis

The sample size was calculated by considering 80% power and 5% level of significance. The data was analysed using SPSS 22 software. Categorical data was represented in the form of frequencies and proportions. Continuous data was represented as mean and standard deviation. The p-value of less than 0.05 was considered statistically significant.

RESULTS

Among one hundred and sixty-four patients, one hundred and sixty patients were analysed. In arm1 fifty-five (n=55) patients received palliative radiation alone to total dose of 30Gy in 10 ractions, five daily fractions per week for two weeks. The arm 2 with fifty-three (n=53) patients were treated with 14.4Gy in 4 fractions, 3.6Gy per fraction, two fractions per day with 6 hours gap after first fraction for two consecutive days. The same schedule was repeated after 4 weeks if the patients had at least partial response and less than grade 2 mucosal and dermal toxicities. The third arm (arm 3) consisting of fifty-two (n=52) patients received modified quad shot regimen in which 14.4gy in 4 fractions, was delivered 3.6Gy per fraction, one fraction per day for 4 consecutive days along with concurrent carboplatin on the first day of radiation. The same schedule repeated 4 weeks apart after clinical response and toxicity assessment.

The patient characteristics with respect to gender, habits, co-morbidities and other parameters were similar and comparable among all three groups. The median age was 57years, 58years and 54 years in arm1, arm2 and arm3 respectively. The most common site was oral cavity representing 67 patients (42.19%), followed by Oropharynx with 37 patients (23.1%), Hypopharynx with 36 patients (22.5%) and larynx with 20 patients (12.5%) (Table1).

Symptom relief and subjective response

The commonest symptom at presentation was pain followed by dysphagia. The maximum pain relief assessed by Visual Analogue Scale (VAS) was observed in arm 2, 82.6% (43/53) followed by 79.2% (41/53) and 72% (39/55) in arm3 and arm1 respectively, however the difference was not statistically significant (p=0.103). The improvement in dysphagia was 64.2% (35/55), 75% (40/53), 75% (39/52) in arm1, arm2 and arm 3 respectively, with statistically insignificant p value (p=0.95) (Table 2).

Radiation mucositis

The number of patients with grade 2 mucositis were 18(36%), 11(20.7%), 12 (23.07%) in arm 1, arm 2, arm 3 respectively. The grade 3 mucositis was 11 (20%), 4 (7.54%), 5(9.6%) in arm 1, arm 2, arm 3 respectively. The difference observed was not statistically significant.

Radiation dermatitis

The grade 2 radiation dermatitis was observed in all three arms. In arm 1, 11(20%) patients and 3.33% in both arm 2 and arm 3 had grade 2 skin reaction. However, this difference was not statistically significant with the value of p=0.121. The grade 3 and above toxicity was not seen in any of the arms.

Response assessment

The response assessment was done by RECIST 1.1 criteria. The number of patients with partial response was 14(25.45%),

19(36.67%), 17(33.33%) in arm 1, arm 2 and arm 3 respectively and this was not found to be statistically significant (p=0.7). None of the patients had complete response. The patients with stable or progressive disease were either referred for palliative chemotherapy or best supportive care depending on performance status and patients' willingness for further therapy.

Quality of Life (QOL)

The quality of life in terms of relief from pain, swallowing difficulty, fatigue and decreased appetite were better all three arms. The scores were better in arm 2 and 3 than arm 1 however the difference was not statistically significant.

Survival analysis

The median survival in arm 1, arm 2 and arm3 was 112 days, 101 days, 132 days respectively. This difference was not statistically significant (p=0.965) (Figure 1).

DISCUSSION

The patients with locally advanced head and neck cancers are generally considered for palliative treatment due to poor performance status and higher tumour burden that are associated with tumour hypoxia and resistant clonogenic cells.

The main objective of palliative treatment is to alleviate the distressing symptoms, improve the quality of life with less toxicity,

Tab. 1. Patient characteristics

Patient Characteristics		Arm 1 (55)	Arm 2 (53)	Arm 3 (52)
Number of patients				
Gender	Male	44(80%)	36 (66.67%)	43 (83.33%)
	female	11 (20%)	17 (33.34%)	9 (16.67%)
Age	Median age	57 years	58 years	54 years
Site	Oral cavity	22	22	25
	Oropharynx	15	14	14
	Hypopharynx	13	11	8
	Larynx	5	6	4
	ECOG 2	14 (46.67%)	23 (76.67%)	16 (53.33%)
Symptoms at presentation	Pain	25	23	24
	Dysphagia	14	13	12
	Fatigue	13	12	12
	Decreased sleep	3	5	4
Stage	IVA	10(33.33%)	10 (33.33%)	11 (36.67%)
	IV B	17 (56.67%)	18 (60%)	17 (56.67%)

Tab. 2. The improvement in dysphagia in arm 1, arm 2, arm 3

		Arm 1 (55)	Arm 2 (53)	Arm 3 (52)	p-Value
Pain		72% (39/55)	82.6% (43/53)	79.20% (41/52)	0.103
Dysphagia		64.20% (35/55)	75% (40/53)	75% (39/52)	0.95
Radiation Mucositis	Gr 2	18 (36%)	11 (20.7%)	12(23.07%)	0.302
	Gr 3	11 (29%)	4(7.54%)	5(9.6%)	0.165
Radiation Dermatitis	Gr1	20 (36.67%)	11 (20%)	12(23.3%)	
	Gr2	7(13.3%)	2 (3.33%)	2 (3.33%)	0.121
Response	CR	0	0	0	-
	PR	14(25.45%)	19(36.67%)	17(33.33%)	0.7
Assessment	SD	31(56.67%)	28(53.3%)	30(56.67%)	0.95
Survival (Median)	-	112 days	101 days	132 days	0.965

*Gr= Grade, CR= Complete response, PR= Partial response, SD=Stable disease

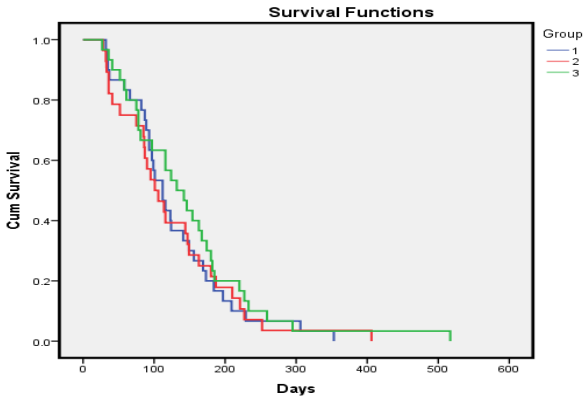

Fig. 1. Kaplan Meir curves for median survival analysis ARM 1 (30Gy/10Fr) ARM 2 (14.4Gy/4Fr) ARM 3 (14.4GY/4Fr +CT)

less hospital stays, possible tumour control and allowing them to spend quality days with their family members. The various palliative RT schedules include 30Gy/10fr, 50Gy/20fr, 20Gy/5fr, 40Gy/16fr, 48Gy/16fr and 14.4Gy/4fr and none of them are recommended as standard schedules. These RT schedules are customized for individual patients that suits best based upon their symptoms, expected survival and socioeconomic needs.

In this study, optimum subjective response and symptom relief of pain, dysphagia, improvement in quality of life and appetite were observed in all the three arms and were comparable. The scales for response and symptom relief were better in arm 2 and 3 than arm 1 but the difference was not sufficient to reach statistical significance. In the study done by Finnegan et al in which 14.8 Gy was delivered in 4 fractions over two days and the improvement in dysphagia and pain relief was 56% and 62% had respectively [12]. In our study the pain relief in arm 1, arm2 and arm3 was 72%, 82.6% and 79.2% respectively. Improvement in dysphagia in arm 1, arm 2 and arm 3 was 64.2%, 75% and 75% respectively. Objective tumour response was comparable in the three arms but statistically not significant.

In the study conducted by Corry [13]. where the QUAD SHOT of 14 Gy was delivered in 4 fractions, twice daily for two days at least 6 hours apart and the same repeated at 4 weekly intervals for a further two courses if there was no tumour progression. Among 16 patients 77% of the population had either stable disease or partial response of which 53% had either a complete or partial response. In our study, arm 1, arm 2, and arm 3 correspondingly showed partial response in 5.45%, 36.67%, and 33.33% and stable illness in 56.67%, 53.37%, and 56.67%.

In our study patients of QUAD shot arms received two sessions in contrary to the studies by Gamez, where three sessions were delivered. All the three arms demonstrated variable tumour response. The number of QUAD shot cycles and inability to complete the treatment were predictors of response.

In terms of toxicity profile, Quad shot regimen with or without chemotherapy had reduced toxicity when compared to conventional schedule with similar tumour BED-38-40 Gy.

The number o f patients with grade 3 mucositis in a rm1, arm2 and arm3 were 11(29%), 4(7.54%), 5(9.6%) respectively which was not statistically significant (p=0.165). These results of our study were similar to the study done by chrn et al which was a single institutional retrospective study to evaluate the effective palliation rt schedules [14]. In this study it was observed that grade 3 and above mucositis was seen in 38% in patients treated with 30 Gy in 10 fr in comparison to 9% in patients treated with RTOG quad shot regimen.

A study by Abhishek the three palliative schedules i,e Quad Shot schedule (14.8Gy/4fr), Christie schedule (50Gy/16 fractions over 3.1 weeks) and conventional palliative schedule of 20Gy/5 fractions were compared and evaluated in terms of tolerability, toxicity and efficacy and 28% of patients experienced grade 3 skin reactions with the quad shot regimen and 44%, and 16% in other groups. In our study, 7(13.3%) of patients in arm 1, 2(3.33%) in arm 2, arm 3 had grade 2 skin reactions. This difference was not statistically significant (p=0.121) [15]. There was no grade 2/3 haematological toxicity observed in any of the arms and the toxicities were comparable to studies by Chen et al and Gamez et al.

The median survival in arm 1, arm 2, arm 3 was 112 days, 101 days and 132 days respectively. The median survival in arm 2 was comparatively low as the majority of the patients had locally advanced disease IVB (69%) compounded by poor performance status (ECOG2=76.67%).

CONCLUSION

Quad shot regimen with or without chemotherapy is comparable with conventional palliative radiation schedule and is associated with adequate symptom relief, better compliance, and manageable toxicity profile. In high volume centres offering oncological services for the patients hailing from distant places, quad shot regimen can be considered instead of conventional 2 weeks palliative 30Gy in 10 fractions without compromising the oncological outcome with manageable toxicity profile. Also, this allows the optimum utilization of radiotherapy resources that are not easily accessible for the treatment of other curable, early-stage malignancies.

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