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Running Title: Quad shot like RT plus CT on quality of life
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Quad Shot Like Radiotherapy with Concurrent Chemotherapy for Advanced Head and Neck Cancer

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Abstract

Background: Improvement in quality of life and palliation of symptoms forms the primary end point in patients unfit for definitive treatment modalities. Quad-shot like radiotherapy aims to achieve these objectives with addition of chemotherapy in advanced head and neck malignancy.

Methods

In this study, patients >18 years of age, with advanced head and neck malignancy (stage IVA&B) in non-nasopharyngeal sub-site, not fit for radical treatment were included in this mono-centric, prospective, interventional study. Quad-shot like regimen of 14.4Gray in 4fractions delivered with concurrent carboplatin (AUC2) on day-1 of radiation cycle and reviewed after 3-weeks. Based on palliative response, total two repetition are done. Quality of life analysis was done with European Organization for Research and Treatment– Head & Neck-35 questionnaire Treatment induced toxicity evaluated with common terminology

criteria for adverse event version 5.0 and radiation therapy oncology group toxicity grading. Treatment outcome was assessed with response evaluation criteria in solid tumors1.1. Microsoft-excel, SPSS version-22 used to analyze data. Kaplan-Meier survival curves were used for overall survival, *P*-value<0.05 with Pearson chi-square test and ANOVA was considered as statistically significant.

Results

The palliation of symptoms and improvement in quality of life were recorded in 80% and sustained up to 3 months, with median overall survival of 8±0.411 months, maximum benefit appreciable with larynx compared to other sub-sites. However, grade-4 toxicity reported with one patient in post phase-1 and two patients in post phase-2 and managed with best supportive care.

Conclusion

Quad-shot like radiotherapy with concurrent chemotherapy for advanced head and cancer found to be beneficial in patients unfit for radical treatment resulting in desirable palliative outcome.

Keywords: Radiation Dose Hypofractionation, Carboplatin, Palliative Care, Quality of Life, Squamous Cell Carcinoma of Head and Neck.

Introduction

Globally, 57.5% of head and neck cancer accounted from Asia and 60-80% of patients present with advanced diseases in India as compared with 40% in developed countries.[1,2,3] Patients with advanced head and neck cancers who are not eligible for curative treatment represent a challenging cohort of patients to manage, given the complexity and severity of their presenting symptoms.[4]

For these patients, palliative care is instrumental in providing pain control, autonomy and dignity for the reminder of

their lives.[5] While palliation is a poorly defined concept, it usually refers to alleviation of symptoms when life expectancy is limited. Palliation is also used as pre-emptive modality in order to maintain an existing level of comfortable autonomy when the disease process is expected to become symptomatic prior to one's demise.[6] The goal of ideal palliation includes optimal symptomatic relief, tumor response, low toxicity and minimization of the time spent in a health care facility or treatment centre.[7]

Radiotherapy (RT) forms an integral part in reaching this palliative goal. The commonly practiced palliative radiotherapy regimen is 8 gray (Gy) in 1 fraction (fr), 20Gy in 5fr, 30Gy in 10fr and 40Gy in 15fr with intention to palliate within reasonable treatment time.[8,9] A cyclical hypofractionated RT known as quad shot, with 14 to 14.8Gy in 4 fractions over 2 consecutive days was formulated originally for advanced pelvic malignancies and has been implemented successfully for palliative treatment of head and neck cancers.[10] Quad-shot is one such palliative radiotherapy regimen able to meet these criteria in head and neck malignancy relative to other fractionation schedules. It used twice daily radiation doses, 3-4 week break before repeating and delivered within two consecutive days.[10,11] In the present study, we have used the same dose per fractionation but delivered it in four consecutive days.

In head and neck squamous cell carcinoma the addition of platinum-based chemotherapy (CT) to radiotherapy (RT) increases 5-year overall survival by about 10% indicating enhancement in response to radiation treatment.[12] Extrapolating this effect of chemotherapy in conjunction with radiotherapy in palliative setting can be beneficial.

Therefore, the present study evaluated the feasibility and outcome of optimal response for palliation, using quad shot like radiotherapy along with chemotherapy in advanced head and neck cancer patients

(stage IVA&B) who are not fit for radical treatment.

Materials and methods

This was a mono-centric single arm prospective interventional study for the assessment of proposed treatment plan in Indian subset of population. This study was approved by the Scientific Review Board and institutional Medical Ethics Committee and assigned as KMIO/MEC/011/23.

A total of 65 study participants, diagnosed of stage IVA&B head and neck carcinoma (American joint committee on cancer-AJCC 8th edition) in non-nasopharyngeal sub-site (oral cavity, oropharynx, maxillary sinus, hypopharynx and larynx subsite) with histologically proven squamous cell carcinoma, who are found to be ineligible for radical treatment as per multi-disciplinary committee were included in the study.

Patients with prior radiation to involved area within 2-years, eastern co-operative oncology group (ECOG)-3&4 or active infection were excluded from the study. An informed written consent was administered to all patients prior to treatment.

Each patient was treated via three-dimensional conformal radiation therapy (3DCRT) with a margin of 1cm to gross tumor volume (GTV). Quad shot regimen of 14.4Gy in 4fr with one fraction per day delivered along with concurrent carboplatin (AUC2) on day-1 of each radiation cycle. The patients were subsequently reviewed after 3 weeks and re-evaluated and patients who responded to treatment were considered for the next cycle of RT and chemotherapy. If the patient developed progressive disease or severe reactions, further cycles were not planned and these patients were managed based on their performance status as per ECOG score, either with palliative chemotherapy or best supportive care. Post-treatment follow up was done monthly up to initial 3 months and then

every 3 months for a minimum period of 2 years. Quality of life (QOL) was assessed before and after each treatment session and also during follow-up for individual patient palliative response evaluation using EORTC-H&N-35 quality of life questionnaire (QLQ) English version & local language (Kannada) version. Treatment induced toxicities evaluated with CTCAEv5.0 and RTOG toxicity grading. Additionally, radiological treatment outcome was assessed with RECIST1.1 using computed tomography scan of involved region.

Statistical analysis

Data were entered into MS excel data sheet and were analyzed using SPSS 22 version software. Categorical data were represented in the form of frequencies and proportions. Continuous data were represented as mean and standard deviation. Graphical representation of data was done with MS excel and MS word to obtain various types of graphs such as bar diagram, pie diagram, and line diagram. The overall survival (OS) was defined as the time duration from the date of diagnosis of the disease till the time the patient was alive. OS was determined using Kaplan Meier survival curves. P-value<0.05 with Pearson chi-square test and ANOVA was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel and SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) were used to analyze data.

Results

The mean age of participants in the study was 55.55 ± 10.242 years and the majority of the participants were in the age group 51 to 60 years (32.30%). Among these patients, 15(23.07%) were female, 49(75.38%) male and 1(1.53%) transgender. In the study, 49(75.38%) were smoker and 42(64.61%) were alcoholics, while 28(43.07%) were betel-nut chewers and 33(50.76%) were tobacco

chewers. In terms of disease localization, 31(47.69%) participants had lesions in oral cavity, 18(27.69%) in oropharynx, 7(10.76%) in hypopharynx, 8(12.30%) in larynx and 1(1.53%) in paranasal sinus. For overall survival analysis one case of maxillary sinus was included in oral cavity group.

In the study, 35(53.84%) patients were in stage 4A and 30(46.15%) were in Stage 4B and all patients had ECOG>2. On histopathological examination, 9(13.84%) Grade-1, 53(81.53%) Grade-2 and 3(4.61%) Grade-3 squamous cell carcinoma were found in the study participants.

Assessment of pre-treatment and post-treatment QOL score at various scheduled intervals [Figure-1] was statistically significant with $P<0.05$.

The palliation of symptoms evaluated in terms of pain score [Figure-2], indicates that highest pain score observed in baseline and lowest in the 2nd and 3rd month (37).

Median swallowing score was 0 from baseline to 6 months, at 9 months score was 6 and at 12 months score was 12 and the median speech score was 0 from baseline to 6 months, at 9 months score was 17 and at 12 months score was 66.

The subsite-wise pain score (Table 1) indicates that proposed treatment protocol benefit varies with disease localization and its graphical illustration (Figure 3) clearly depicts the impact of the treatment.

Overall survival: In the study, in the 1st month 64(98.46%) of the patients were alive, in the 2nd month 63(96.92%), in the 3rd month 56(86.15%), in the 6th month 37(56.92%), in the 9th month 24(36.92%) were alive and in the 12th month 14(21.53%) patients were alive while none of the patients survived beyond 14 months.

The benefit of treatment, in terms of overall survival varied with each sub-site assessed in this study (Figure 4) with median survival time was 8±0.411months and maximum response observed in larynx.

As per RECIST1.1 criteria, none of the patients had partial or complete response. The majority of the patients had stable disease in the 1st follow-up (100%). In the 3rd month, 23(35.38%) of the patients had progression and 11(16.92%) had progression in the 6th month follow-up.

Progression-free survival: In the 3rd month, the progression-free survival was highest for oropharynx tumours and lowest for oral cavity tumours. The progression-free survival in the 6th month was highest for laryngeal tumours and lowest for oral cavity tumours.

Treatment induced toxicity (Table 2): In the post phase-1 after 3 weeks, 9(13.84%) had grade 2 toxicity, 1(1.53%) had grade 3 and grade 4 toxicity, respectively. During the 1st month, post phase-2, 5(7.81%) had grade 2 toxicity, 3(4.68%) had grade 3 and 2(3.12%) had grade 4 toxicity.

Haematological toxicity: In phase-1, 16(24.6%) patients had grade 2 haematological toxicity; in phase-2, 3(4.617%) patients had grade 1 and 1(1.53%) had grade 2 toxicity. At other intervals of follow-up, there was no incidence of haematological toxicity.

Discussion

Our study shows improvement in the overall quality of life score and pain score compared with other parameters, with maximum benefit seen in larynx compared with other study sub-sites and sustained up to 3-6 months. The progression-free survival was highest for oropharynx tumours, with none of the patient having hematological toxicity > Grade 2.

The aim of palliative radiation in any advanced cancer is to relieve the symptoms quickly while minimizing the toxicity. In addition, the treatment should be delivered in the shortest possible time considering patient and caregivers convenience. To do so, 30Gy/10fr is the most practiced palliative radiation regimen around the world. But in recent times, the effectiveness of quad shot regimen is

successfully evaluated to further titrate the treatment benefit.[13]

Lok et al. found that "for patients with incurable malignant disease in the head and neck, the palliative RTOG 8502 quad shot regimen of 14.4Gy in 4fr for 3 cycles for a total dose of 44.4Gy provides excellent rates of palliative response with minimal associated toxicity.[14] Patients who are able to complete greater number of RT cycles have higher rates of palliative response and overall survival". Akansha et al. compared 30Gy/10fr with quad shot (14.4Gy in 4fr) in advanced head and neck cancers and found symptom relief was similar among the two schedules with overall response seen in majority (>70%) of the patients in both the groups with treatment well tolerated.[13]

The key difference between these trials and our study is that, treatment consisted of twice daily fractionation in former trials and did not include any form of chemotherapy agents and since equivalent response is observed, we have conducted single arm study to evaluate the response of quad shot like RT dose with once daily fractionation, along with addition of radio-sensitising chemotherapy.[13] We did not give the third cycle of quad shot regimen, as none of our patients showed objective response after the second cycle.

Singh et al. compared two weeks versus four weeks gap in quad shot regimen in locally advanced head and neck cancers and found no difference with overall palliation achieved in terms of symptomatic response and loco-regional control. In our study, we have used a gap of 3 weeks between the quad shots.[15]

Velu et al. assessed repetition of palliative split course radiotherapy of 22.5Gy in 5 fractions with a gap of 4 weeks for locally advanced squamous cell carcinoma and found 25% excellent symptomatic relief, 26% good symptomatic relief and 31% partial relief.[16] Traditionally practiced 30Gy in 10fr has an EQD2.

(2Gy equivalent dose) of 32.50Gy and biological effective dose (BED) of 39.00Gy while EQD2 and BED of quad shot like radiotherapy is 16.32Gy and 19.58Gy. Similar to the study by Velu et al. we used dose per fraction of quad shot with gap of 3 weeks and overall, twice repetition yielding up to similar BED and EQD2 of 30Gy/10fr.[16]

Gamez et al. found quad shot palliative radiation therapy coupled with radio-sensitizing chemotherapy improves the quality of life in patients with newly diagnosed or recurrent head and neck cancer not amenable to curative therapy, while Upadhyay et al. analyzed effectiveness of addition of immune checkpoint inhibitors with palliative quad shot radiation therapy in head and neck cancer and found improved local control compared with radiotherapy alone.[17,18]

In our trial, we have used carboplatin as radio-sensitising chemotherapy and there is no addition of immunotherapy. And most importantly our trial is one of a kind, since we have evaluated the response of quad shot with radiosensitizer in Indian subset of population with respect to palliation of symptoms and also assessed the efficacy in terms of reduction in intake of pain medications.

The present study revealed that quad shot regimen was able to produce palliation of symptoms and improvement in QOL in 80% of the patients studied and it was sustained up to 3 months post RT followed by which gradually there is an increase in their symptom score which correlated with the disease progression in our study, these results are quite comparable to study done by Lok et al.[14] Despite including patients with advanced disease burden, and limited longevity, we report prolonged median survival of 8 ± 0.411 months, respectively. The overall survival was highest for laryngeal tumours with 9.8 months and lowest for oral cavity tumours with 7.9 months in our study, with maximum benefit was in the reduction of pain compared with other parameters assessed.

In our study, 98% of the patients completed the second phase, indicating the tolerability and feasibility of the treatment, and related to a greater palliative treatment response and better outcomes with none of the patient reported grades 3 or 4 hematological toxicity which is comparable to the study by Gamez et al.[17] However, there was one patient post phase 1 reported of grade IV toxicity and 2 patients reported grade IV toxicity at 1st month and managed with best supportive care.

The limitations of our trial and similar trials reported in the literature are that they are single armed studies, which preclude any comparison with the conventional schedules of radiation.

Conclusion

Hypofractionated palliative radiotherapy using quad shot regimen with concurrent radio-sensitizing chemotherapy for advanced head and cancer was found to be beneficial in palliation of symptoms and in improving quality of life, in patients unfit for radical treatment with acceptable toxicity profile.

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Conflict of interest: None.

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Authors' Contributions:

Poornachandra Tejaswi Siddappa: Study design, data gathering, drafting and reviewing the manuscript

Shamsundar Sunkappa: Data gathering and reviewing the manuscript

Jagannath Kunigal puttaswamy: Data gathering and reviewing the manuscript

Nanda Ramanand: Drafting and reviewing the manuscript

Aradhana Katke: Drafting and reviewing the manuscript

Thejaswini Boraiah: Drafting and reviewing the manuscript

All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figure-1: Comparison of quality of life (QOL) score during various treatment stages and follow-up period shows, the treatment effect sustained up to 3-6 months with median overall QOL score recorded as 50.

Figure 1: Comparison of quality of life (QOL) score during various treatment stages and follow-up period shows the effect of the treatment sustained up to 3-6 months with median overall QOL score recorded as 50.

Figure-2: Comparison of pain score at various phases of treatment and follow-up shows betterment in terms of pain score maintained up to 1st 3months, followed by pain score similar to post initial phase of quad shot sustaining till 6months.

Figure 2: Comparison of pain score at various phases of treatment and follow-up shows betterment in terms of pain score maintained up to the 1st 3months, followed by pain score similar to post initial phase of quad shot sustaining till 6 months.

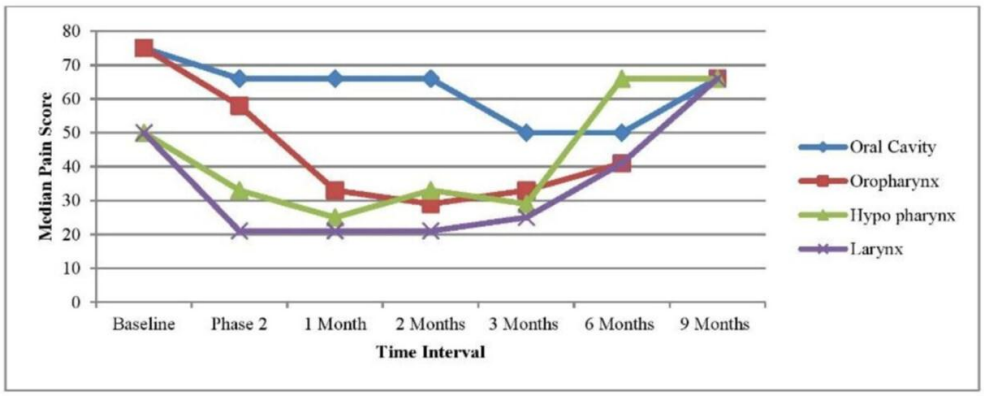

Figure-3: Line diagram showing correlation of pain score with respect to sub-site. The proposed treatment protocol benefitted larynx to maximum extent followed by hypopharynx and oropharynx, with least effect in oral cavity tumours.

Figure 3: Line diagram showing correlation of pain score with respect to sub-site. The proposed treatment protocol benefitted larynx to maximum extent followed by hypopharynx and oropharynx, with least effect in oral cavity tumors.

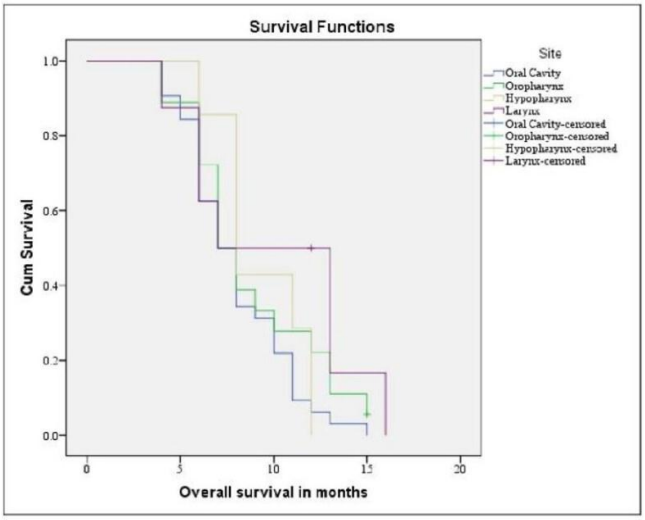

Figure 4: Kaplan meier survival curve showing overall survival with respect to sub-site. The proposed treatment regimen was beneficial in laryngeal tumors followed by hypopharynx and oropharynx, with least survival benefit seen in oral cavity tumours.

Figure 4: Kaplan-Meier survival curve showing overall survival with respect to sub-site. The proposed treatment regimen was beneficial in laryngeal tumors followed by hypopharynx and oropharynx, with least survival benefit seen in oral cavity tumors.

Table 1: Correlation of pain score with respect to subsite

	Site			
	Oral Cavity	Oropharynx	Hypo pharynx	Larynx
	Median	Median	Median	Median
Baseline	75	75	50	50
Phase 2	66	58	33	21
1 Month	66	33	25	21
2 Months	66	29	33	21
3 Months	50	33	29	25
6 Months	50	41	66	41
9 Months	66	66	66	66
12 Months		58		66

Table 2: Comparison of toxicity chart at phase 1, 1st month, 2nd month, 3rd month, 6th month and 9th month

Toxicity grade		0		1		2		3		4	
	Total patients	Count	%	Count	%	Count	%	Count	%	Count	%
3 weeks postphase1(P1)	65	54	83.07%	0	0.0%	9	13.84%	1	1.53%	1	1.53%
1 Month postphase2(P2)	64	54	84.37%	0	0.0%	5	7.81%	3	4.68%	2	3.12%
2 Month	63	59	93.65%	4	6.34%	0	0.0%	0	0.0%	0	0.0%
3 Months	56	52	92.85%	2	3.57%	2	3.57%	0	0.0%	0	0.0%
6 Months	37	33	89.18%	0	0.0%	4	10.81%	0	0.0%	0	0.0%
9 Months	24	21	87.50%	0	0.0%	3	12.50%	0	0.0%	0	0.0%
12 Months	14	12	85.71%	0	0.0%	2	14.28%	0	0.0%	0	0.0%

As per the above data, none of the patients experienced grade 3 and grade 4 toxicity in follow-up.