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Research article

The patient-reported outcome measures in oropharyngeal, laryngeal and hypopharyngeal cancer patients treated with Volumetric Modulated Arc based simultaneous integrated boost radiotherapy

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ABSTRACT

Objective: To assess the change in the quality of life (QOL) in head and neck cancer patients treated with Simultaneous Integrated Boost (SIB) by Volumetric Modulated Arc Therapy (VMAT) technique.

Methods: Thirty patients with localised head and neck cancers (Stage II–IVa) were treated with VMAT and SIB technique. The three-dose levels prescribed were 68.2 Gy at 2.2 Gy/fraction, 62 Gy at 2 Gy/fraction and 55.8 Gy at 1.8 Gy/fraction to the high, intermediate and low-risk volumes respectively. Concurrent chemotherapy with cisplatin 100 mg/m² was administered once in three weeks. Acute toxicities were evaluated and scored according to the RTOG grading system. Quality of life (QOL) was assessed using European Organization of Research and Treatment of Cancer (EORTC) QLQC30 and HN35 questionnaires at baseline and in three instances (immediately, one month and three months after the radiotherapy).

Results: Out of the total 30, 80% patients had a complete response (CR) at the median follow up of 12 months, while three patients died because of progression, and the remaining 3 had stable disease. All planning objectives were achieved for organs at risk and planning target volume (PTV). There was a statistically significant (p value < 0.001) reduction in global quality of life scores at the end of treatment when compared to baseline scores, but by three months, there was the return in the QOL scores in most scales similar to the baseline value.

Conclusion: VMAT based Simultaneous boost radiotherapy is a feasible and safe strategy in terms of toxicity profile with an acceptable transient change in the quality of life and allows a faster return to baseline quality of life.

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Introduction

Head and neck malignancies are one of the most prevalent cancers observed in India with a global burden of 5,50,000 per annum [1]. Radiation therapy forms one of the primary modalities of their treatment. Conventional radiotherapy is usually delivered over a total duration of seven weeks at a dose of 180–200 cGy per day for five days in a week. The primary cause of treatment failure in head and neck cancers is the accelerated repopulation by the tumour cells during conventional radiotherapy. It will be further enhanced if the overall treatment time is prolonged [2–3]. There-

fore by reducing the overall treatment time, it would be possible to improve tumour control by minimising clonogenic tumour regeneration [4]. Various trials like Polish, Concomitant Boost and CHART have addressed this issue by different fractionation strategies, albeit at the cost of increased treatment-related toxicities [3]. The Simultaneous Integrated Boost (SIB) technique represents an innovative way of investigating the role of accelerated fractionation [5]. Volumetric Modulated Arc Therapy (VMAT) is a novel radiation treatment technique that is based on volumetric modulated rotational delivery, as opposed to classic Intensity Modulated Radiotherapy (IMRT), which uses fixed gantry beams. By varying the speed of gantry rotation, multileaf collimator shape and continuously changing the fluence (dose rate), VMAT delivers highly conformal IMRT plans in a short time [6–9].

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Disease control, toxicities and survival have been the traditional endpoints of any study in cancer patients. Health-related quality of life (HR-QOL) is one parameter that is usually not studied, but it is a significant additional endpoint nowadays [10]. Cella et al. [11] defined the quality of life (QOL) as “a patient’s appraisal of and satisfaction with their current level of functioning as compared to what they perceive to be possible or ideal.” Patients who suffer from head and neck malignancies have more debilitating problems such as difficulty in swallowing, speech, and hearing impairment and therefore, QOL assessment is essential for them [12–14]. Studies on quality of life of head and neck cancer patients managed with routine treatment schedules are plenty in number. Although toxicity profile and early outcomes of this novel SIB technique with VMAT has been explored already, there is a lack of data exploring the patient-reported QOL with SIB and VMAT [15–17]. Moreover, the quality of life can be improved significantly with advances in conformal radiotherapy techniques as suggested by numerous studies [18–21]. Patient-reported outcome measures (PROMs) are increasingly being utilised in the clinical settings and are more reliable than the subjective assessments by clinicians. Although there are various methods available for assessing the quality of life, The European Organisation of Research and Treatment of Cancer Quality of Life Core Questionnaire, version 3.0 (EORTC QLQC30) and EORTC head and neck module (EORTC QLQ-HN35) is a more reliable and robust questionnaire and has been validated in multiple studies [22,23]. Thus, the primary intent of this study is to assess the change in QOL in patients of head and neck cancer managed with simultaneous integrated boost radiotherapy by VMAT. Our secondary objective is to report the clinical outcomes of this novel-treatment in the form of local tumour control.

Materials and methods

Patient grouping

All consecutive patients of squamous cell carcinomas of head and neck who presented to the Department of Radiotherapy, in our institution between December 2014 and July 2015 and who satisfied the inclusion criteria were included in the study. Informed consent regarding chemotherapy and the procedure of VMAT was obtained. The patients were treated with SIB VMAT, and the results were analysed and tabulated.

Target delineation

After CT simulation, contouring was done according to International Commission on Radiation Units, and Measurements (ICRU) Reports 50 and 62, target volumes were defined Planning target volumes (GTV and CTV) and organ at risk volumes (e.g., spinal cord and both the parotids) to be contoured on each slice.

Three PTVs to be created

PTV(HR)-clinically and radiologically demonstrable tumours, including the involved nodes.

PTV(IR)-the areas considered to be at high risk of subclinical disease extension including the nodal levels considered to be at high risk of having metastatic disease.

PTV(LR)-nodal drainage areas considered to be at low risk for having nodal involvement.

Dose prescription was based on RTOG 0226 protocol PTV was divided into

PTV high risk-68.2 Gy/31 fractions,

PTV intermediate risk- 62 Gy/31 fractions and
PTV low risk-55.8 Gy/31 fractions.

The maximum permissible point doses to the spinal cord were planned below 45 Gy. The biological equivalent dose (BED) for tumour control was calculated as 83.2 Gy10 whereas for late reacting normal tissue it was calculated as 103.3 Gy3. The linear-quadratic model was used to calculate the BED.

Quality of life scoring

The European Organization of Research and Treatment of Cancer Quality of Life Core Questionnaire, version 3.0 (EORTC QLQC30) and EORTC head and neck module (EORTC QLQ-HN35) were used to assess the change in QOL. The scoring was done pre-treatment, at the completion of therapy, one month, and three months post-therapy. The EORTC QLQC30 contains the following parameters (Table 1).

The EORTC QLQ-HN35 includes the following components (Table 2).

The principle for scoring these scales is based on the instruction in the scoring manual of EORTC.

- o Initially, the raw score for each scale is calculated by obtaining the average of the items that contribute to the scale.
- o Then, a linear transformation is used to standardise the raw score, so that scores range from 0 to 100
- o A high score for a functional scale represents a high/healthy level of functioning,
- o A high score for the global health status / QoL represents a high QoL,
- o A high score for a symptom scale/item represents a high level of symptomatology/problems

Statistical analysis

Patient characteristics and local control were described using frequency tables with counts and percentages. The normality test was applied to the quality of life scores, and the scores showed a non-normal distribution. So, non-parametric tests were used to do the analysis. The quality of life scores (median and range) were calculated at various time points and compared to baseline values using the Friedmann test. The Friedman test is the non-parametric alternative to the one-way ANOVA with repeated measures. It is used to test for differences between groups when the dependent variable being measured is ordinal. All statistical analyses were carried out for two-tailed significance at 5% level of significance with p-value < 0.05 being considered as significant.

Results

Thirty consecutive patients treated with SIB radiotherapy by VMAT participated in the study by completing the questionnaires.

Table 1
Scales in the general questionnaire (EORTC QLQC30).

EORTC QLQ C30			
FUNCTIONAL SCALES	SYMPTOM SCALES	SINGLE ITEMS	
Physical functioning	Fatigue	Dyspnoea	Global QOL
Role functioning	Pain	Insomnia	
Cognitive functioning	Nausea/Vomiting	Appetite loss	
Emotional functioning		Constipation	
Social functioning		Diarrhoea	
		Financial difficulties	

Table 2
Scales in the EORTC QLQ HN35 module.

EORTC QLQ HN 35		
MULTIPLE ITEM SCALES	SINGLE ITEM SCALES	
Pain	Teeth	Pain killers
Swallowing	Mouth opening	Nutritional Supplements
Senses	Dry mouth	Feeding tube
Speech	Stick y saliva	Weight loss
Social eating	Coughing	Weight gain
Social contact	Felt ill	
Sexuality		

Table 3
Patient characteristics (n = 30).

	No. of patients	% of patients
Sex		
Male	20	67
Female	10	34
Age		
Median	50 years	
Range	14–64 years	
PS		
1	16	64
2	14	46
Site		
Nasopharynx	3	10
Oropharynx	6	20
Hypopharynx	6	20
Larynx	8	26
Oral cavity	7	24
AJCC staging		
Stage II	5	17
Stage III	6	20
Stage IV	19	63
Habits		
Smoking	4	13
Smoking, alcohol & tobacco chewing	15	50
Feeding tube		
Yes	3	10
No	27	90
Chemo received		
Yes	24	80
No	6	20

The patient characteristics in terms of age, sex, site and stage are shown in Table 3.

Patient characteristics

The median age of the treated patients was 50 (range 14–64). Twenty patients (67%) were males. There were about equal numbers of patients of oropharyngeal, laryngeal and hypopharyngeal cancers. Majority of the patients were in stage IV (50%). All patients (100%) received the fractionation regimen according to the specified protocol. Twenty-four patients (80%) received concurrent chemo-radiation with cisplatin. The mean duration of radiotherapy was 51 calendar days for 31 fractions (Range 47–59 days). The mean break in radiation was nine calendar days (Range 4–16 days) which were due to either machine breaks or intervening holidays. None of the patients had a treatment break due to acute toxicities. Nearly half (43%) of patients had habits of smoking, consuming alcohol and chewing tobacco.

The treatment response was assessed at 12 weeks after the radiotherapy by imaging. Complete response was achieved in twenty-two patients, and five patients have achieved a partial response. There was a progressive disease at the primary site for

three patients. One patient died of aspiration pneumonia. At three months post-radiotherapy, complete response was seen in twenty-four patients, including the one managed with salvage surgery. At 12 months post-treatment, the number of disease-free patients decreased to twenty due to the development of recurrence in four patients.

All 30 cases enrolled in the study filled the first quality of life measurement (100%) before starting treatment. One patient died of aspiration for which quality of life assessment was not done. There were no other drop-outs in the follow-up. The questionnaire was obtained in the local language from the EORTC website after registration. It took around 15–30 min to complete the EORTC questionnaire.

The calculated quality of life scores at various time points such as baseline, at the completion of therapy, one month, three months for the QLQC30 and HN 35 module are shown in Tables 4 and 5. In virtually all parameters, there was worsening of scores after therapy, but at the end of 3 months' post-therapy, there is a return to the almost pre-treatment level (Figs. 1 and 2).

In EORTC QLQ C30, cognitive had the highest score, and the social and role functioning had the lowest score at three months among the functional scales. The median score of global health scale at three months was calculated as 67. In EORTC QLQ C30, the highest scores were found for financial difficulties and fatigue at three months among the symptom scales. The highest ratings were found for dry mouth and sticky saliva at 3 months among the symptom scales in HN 35 module. So, among the C30 QLQ, there is an improvement in all the parameters except social and financial difficulties. The latter two parameters attained the baseline value after three months of treatment and did not worsen further (Fig. 3). Similarly, among the fourteen HN parameters analysed, virtually most of the parameters demonstrated improving trend (Fig. 4). The speech problem, dry mouth, sticky saliva scores demonstrated; however, a worsening trend comparing to three months post-therapy.

Comparing the change in the QOL EORTC scores before initiating treatment and at the end of treatment

On statistical analysis using Friedmann test, it was found that, in EORTC QLQ C30, There was a statistically significant deterioration ($p < 0.05$) of most of the parameters at the end of the treatment except in fatigue, vomiting and constipation as evident from the second column of (Table 4). In this case, p value < 0.05 means worsening scores. This is certainly expected at the end of treatment when the radiation-related toxicity will be at the peak before getting better.

Comparing the change in the QOL EORTC scores between pre-treatment to 3 months post-treatment

On analysis between the quality of life scores between pre-treatment and 3 months post-therapy, most of the parameters did not show statistical significance which indicates that the scores at 3 months following treatment were like baseline scores as shown in the third column of (Table 4). Thus, the patients reached their baseline scores three months following treatment. Global health, role, emotional functioning scales improved significantly ($p < 0.05$) on the analysis between baseline scores and three months' post-treatment scores. In contrary to mentioned in the previous paragraph here p value < 0.05 means scores are improving.

Similarly, in EORTC QLQ HN35, the quality of life worsened at the end of the treatment before getting better by three months after finishing the radiation (Table 5). As discussed before, if the parameters in the third column (baseline vs three months) did

Table 4
Quality of life scores in the general questionnaire and change in quality of life from baseline to 3 months in EORTC QLQ C30 (Friedmann test).

Parameters	Pre Treatment		At the end of Treatment		Post Treatment 1 month		Post Treatment 3 months		Baseline Vs. End of Treatment	Baseline Vs. Three months
	Median	Range	Median	Range	Median	Range	Median	Range	p-value	p-value
Physical Role	80	50–100	53	27–73	53	27–87	87	50–100	<0.001	>0.05
Emotional	58	0–100	17	0–67	33	17–83	67	33–100	<0.01	<0.05
Cognitive	62	33–100	33	0–67	42	8–92	83	8–100	<0.02	<0.05
Social	83	50–100	50	33–83	67	33–83	100	33–100	<0.001	>0.05
Global health scale	67	17–100	17	0–67	33	17–83	67	33–100	<0.001	>0.05
Fatigue	50	8–92	25	0–58	33	17–83	67	17–92	<0.001	<0.001
Nausea, Vomiting	44	0–89	56	11–100	56	11–89	33	22–89	>0.05	>0.05
PainC30	24	0–33	24	0–100	5	0–67	1	0–33	>0.05	>0.05
Dyspnoea	33	0–100	67	25–100	33	17–83	17	0–83	<0.001	<0.001
Insomnia	6	0–100	0	0–67	0	0	0	0	–	–
Appetite loss	16	0–67	81	33–100	67	33–67	0	0–67	<0.001	>0.05
Constipation	33	0–67	33	0–100	0	0–67	0	0–67	<0.01	>0.05
Diarrhoea	0	0–67	0	0–100	0	0–67	0	0	>0.05	>0.05
Financial difficulties	0	0–33	0	0	0	0	0	0	–	–
	33	0–100	67	0–100	67	0–100	33	0–100	<0.001	>0.05

Table 5
Quality of life scores in the HN 35 module and change in quality of life from baseline to 3 months in EORTC QLQ HN35 (Friedmann test).

Parameters	Pre Treatment		At the end of treatment		Post Treatment 1 month		Post Treatment 3 months		Baseline Vs. End of Treatment	Baseline Vs. 3 months
	Median	Range	Median	Range	Median	Range	Median	Range	p-value	p-value
PainHN35	33	0–100	67	25–100	33	17–83	17	0–83	<0.001	<0.05
Swallowing	17	0–92	58	8–100	50	8–100	8	0–92	<0.001	>0.05
Speech Problem	0	0–100	56	0–100	33	0–78	11	0–78	<0.001	>0.05
Senses Problem	0	0–17	33	0–100	33	0–83	0	0–67	<0.001	<0.05
Trouble with social eating	17	0–83	58	8–93	42	8–92	11	0–58	<0.001	>0.05
Trouble with social contact	13	0–73	60	13–93	53	13–80	11	0–73	<0.001	>0.05
Less sexuality	0	0–33	67	17–100	50	17–83	0	0–67	<0.001	>0.05
Teeth problem	0	0	0	0	0	0	0	0	–	–
Opening mouth	0	0–67	0	0–67	0	0–67	0	0	>0.608	>0.05
Dry mouth	0	0–33	33	33–100	33	33–67	33	33–67	<0.001	<0.001
Sticky saliva	0	0–33	67	33–100	67	33–100	33	0–67	<0.001	<0.05
Coughing	0	0–67	33	0–100	0	0–67	0	0–100	>0.05	>0.05
Felt ill	33	0–100	100	33–100	67	33–100	0	0–100	<0.001	>0.05
Pain killers	0	0–100	100	0–100	0	0–100	0	0–100	<0.05	>0.05
Nutritional Supplements	0	0	0	0–100	0	0–100	0	0–100	>0.05	>0.05
Feeding tube	0	0	0	0–100	0	0–100	0	0	>0.05	>0.05
Weight loss	100	0–100	100	100	0	0–100	0	0	<0.05	<0.001
Weight Gain	0	0	0	0	0	0–100	100	100	>0.05	<0.001

not show statistical significance ($p < 0.05$), it indicates the patients reached their baseline scores. If statistically significant, they are getting better in that particular parameter (e.g., Pain, weight loss, dry mouth).

Discussion

Surgery and radiotherapy are the primary mode of management that have been used for many years to achieve disease control in head and neck cancers. Conventional radiation is usually delivered at 180–200 cGy per for five days a week over the duration of six to seven weeks. But, the disease control and survival have not improved with conventional radiotherapy with less than 30% of patients being cured [24]. Further, it was found that accelerated tumour cell repopulation in squamous cell cancers of the head and neck during radiotherapy treatment was responsible for the failure of treatment (3). This poor outcome had led to the use of altered fractionation regimens or concurrent chemo-radiation in malignancies of head and neck. SIB-VMAT helps to counter accelerated repopulation because it results in reduced overall treatment time and radiobiologically improves tumour kill because of the

increase in the fraction size (hypofractionation) over the High-risk dose volume.

Mohan et al. in his landmark trial compared sequential two-phase IMRT and SIB-IMRT and concluded that though both are comparable in sparing the parotids and coverage of the gross disease, the latter is more conformal when it comes of dose distribution. Dose to normal tissues outside the tumour volume is lower for the SIB plan than for the two-phase IMRT plan [5]. He added that the biologically effective dose would be still lower to the normal tissues. This may allow escalation of biologically equivalent dose to the tumour.

Recently, in head and neck malignancies, quality of life has become essential in deciding the treatment modality apart from other routine parameters, and many investigators have published their results on quality of life Studies that have prospectively reported QOL in patients who suffer from malignancies of head and neck. Further, prospective QOL studies focusing on altered fractionation with VMAT are still minimal. Thus, the primary rationale for carrying out this study was to determine the extent and degree of deterioration and eventual recovery of health-related quality of life following treatment with VMAT based simultaneous integrated boost radiotherapy. In the present study, we assessed the health-related quality of life at various time points such as

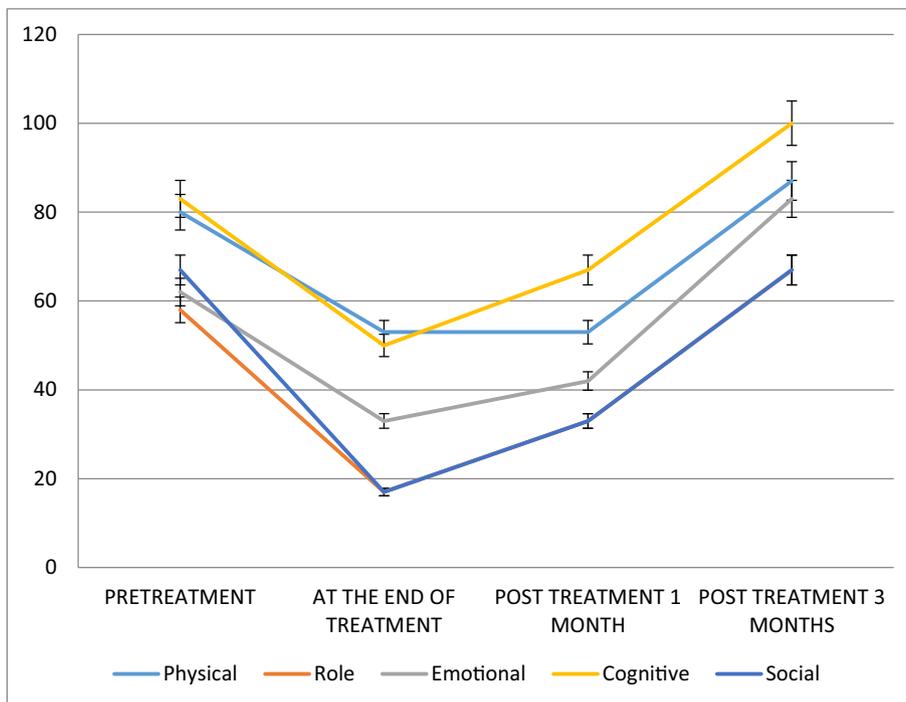


Fig. 1. QOL scores over time from baseline to 3 months for functional scales.

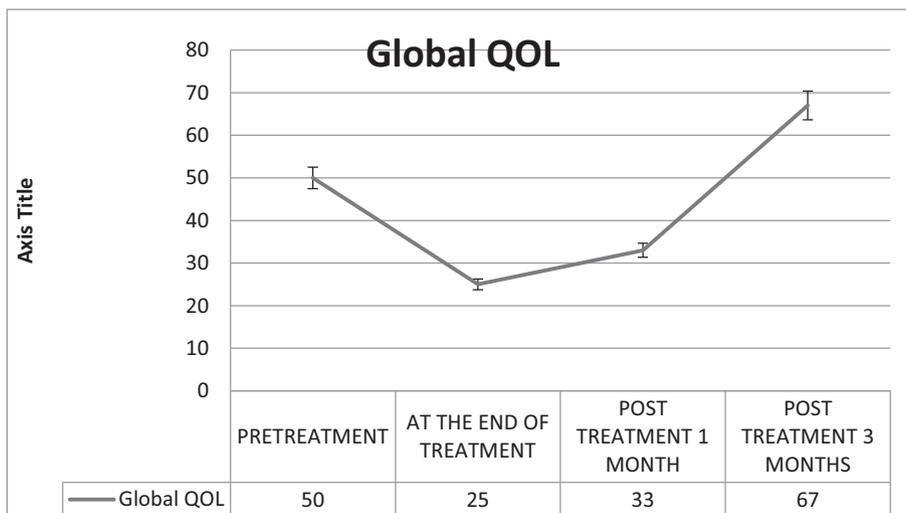


Fig. 2. Global QOL score over time from baseline to 3 months.

baseline, at the end of therapy, one month, three months post-therapy using EORTC questionnaires.

According to Osoba et al. > 20 points change in the score was considered a large effect, and < 10 points change was considered a small effect in the quality of life. A change in the score between 10 and 20 points was called a moderate impact on the quality of life. Based on this, in the present study, we found that in EORTC QLQ C30, the global health scale, the functional scales and most of the symptom scales showed a moderate change in the quality of life (>10 points) at the end of therapy. Similarly, in EORTC QLQ HN35, there was a moderate change (>10 points) at the end of therapy among most of the scales except in two single-item questions (opening mouth, nutritional supplements and teeth problems) [25]. Though the scores worsen during therapy, at the end of 3 months post-therapy, there is a return to almost pre-

treatment levels. This may indicate that with this technique of radiotherapy, the process of normal tissue damage is much less. With added tumour response, there is an improvement in the patient's quality of life during the follow-up period. More importantly, we have shown that SIB-VMAT is a feasible and safe strategy for head and neck cancer patients.

One limitation of our study is the small sample size, and only three months follow up, which limit us to know about the long term toxicity, which is crucial in head and neck cancer patients. Although some of the scores are statistically significant, whether it would be translated into the real clinical benefit is questionable. Also, we don't have any comparator arm to compare the QOL scores in conventional fractionation schedule. Nevertheless it serves its purpose as a feasibility study showing that patient-reported QOL can be implemented in the routine clinic.

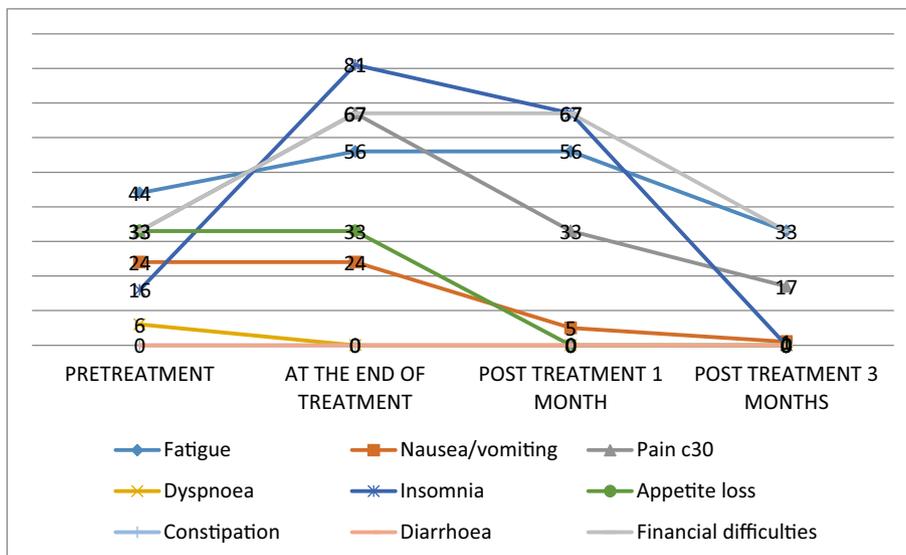


Fig. 3. QOL scores over time from baseline to 3 months for symptom scales in the general questionnaire.

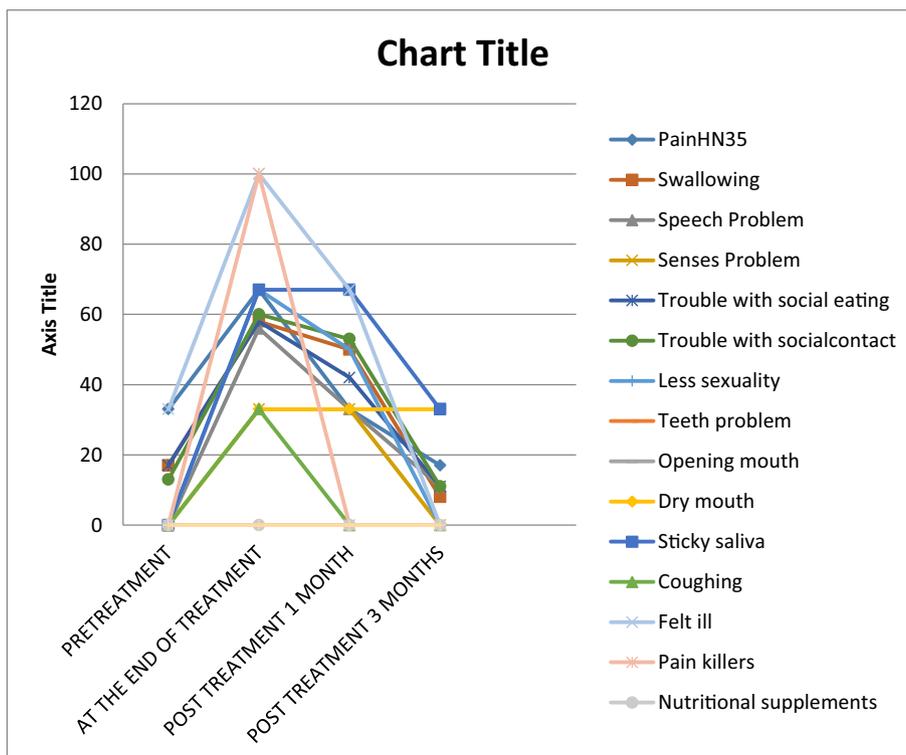


Fig. 4. QOL scores over time from baseline to 3 months for symptom scales in the HN35 module questionnaire.

Conclusion

Use of Volumetric Modulated SIB radiotherapy helps in reducing the dose to organs at risk thereby allowing completion of treatment with less toxicity and faster healing which along with the higher doses to the target volume could enable achievement of better responses. It allows for a rapid return to or even an improvement over the baseline Quality of Life (QOL).

Disclosures

No industry relationships to disclose.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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