RESEARCH ARTICLE

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# Comparative Study of Dysphagia-optimized Intensity Modulated Radiotherapy (Do-IMRT) and Standard Intensity Modulated Radiotherapy (S-IMRT) and Its Clinical Correlation in Head and Neck Cancer Patients

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## Abstract

**Objective:** Dosimetric sparing of critical swallowing structures like constrictor muscles and larynx can lead to improved functional outcomes in head and neck cancer patients treated by chemoradiation. **Methods:** A total of 50 Patients with newly diagnosed, biopsy proven AJCC stage II–IV head and neck squamous cell cancers (HNSCC) were prospectively studied. 25 patients were randomized in each arm of Dysphagia-optimized Intensity Modulated Radiotherapy (Do-IMRT) arm and Standard Intensity Modulated Radiotherapy (SIMRT) arm. Additional dose constraints were applied to the dysphagia/aspiration at risk structures (DARS) in Do-IMRT arm. The impact of using Do-IMRT was assessed by the difference in mean scores of MD Anderson Dysphagia Inventory (MDADI), University of Washington-Quality of Life (UW-QOL), and 100 ml Water Swallow Test (WST). **Results:** Patients in both arms showed significant ($P < 0.01$ or $P < 0.001$) improvement in MDADI (global and composite), UW-QOL and Water Swallow Test scores. However, the improvements were found significantly higher in Do-IMRT as compared to S-IMRT. Significant improvements i.e. mean change from baseline to 12 months ($P < 0.05$ or $P < 0.01$ or $P < 0.001$) were 19. 2, 8.6, 14.3, 7.4, 18.6 and 22.0% higher respectively in Do-IMRT as compared to S-IMRT in MDADI global and composite scores, UW-QOL swallowing scores, and 100 ml Water Swallow (swallowing volume, swallowing capacity and swallowing speed) test scores. **Conclusion:** The Do-IMRT improves swallowing functions compared to S-IMRT in HNSCC patients treated with radical chemoradiation.

**Keywords:** Head and neck cancer- intensity-modulated radiotherapy- dysphagia- quality of life- toxicity

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## Introduction

Dysphagia prevailing for long time following primary chemoradiation (CRT) has negative impact on quality of life in patients of head neck cancer (HNC) treated by chemoradiation (Nam et al., 2005).

As documented in randomized studies, due to modulation in the radiation fluence, intensity modulated radiotherapy (IMRT) delivers highly conformal dose to the tumor by a very concave dose distribution that aids in dose escalation, better target coverage and reduced dose to critical structures thereby improving functional outcomes in terms of dysphagia and aspiration (Ghosh et al., 2021). It has been documented that radiation dose to critical structures involved in the swallowing mechanism resulting in pharyngoesophageal strictures contributes significantly poor long term functional outcome and may lead to long term feeding tube dependency and decreased overall survival (Friedes et al., 2020). Identifying the structures involved in the mechanism of swallowing whose damage causes dysphagia and aspiration related complications and sparing them by using IMRT technique shall produce a tremendous influence on the patient's quality of life post CRT. In patients post chemoradiation, reduced strength of musculature involved in swallowing functions as well as pharyngeal stasis has been seen on barium swallow tests (Nguyen et al., 2007).

This led to the concept of Dysphagia-optimized IMRT (Do-IMRT) where apart from sparing the regional organs at risk, we reduce the radiation dose delivered to structures involved in swallowing, i.e., DARS (dysphagia/aspiration at risk structures) leading to even lesser complications and

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improved quality of life.

In this study our aim was to determine impact of using Do-IMRT on swallowing function and quality of life (QOL) compared to standard IMRT (SIMRT) where dose to DARS was not constrained in HNC patients treated by concurrent chemoradiation. It was qualitatively and quantitatively assessed by MD Anderson Dysphagia Inventory (MDADI) (Chen et al., 2001), University of Washington Quality of Life questionnaires (UW-QOL) (Rogers et al., 2002) and 100ml Water swallow test (WST)(Vermaire et al., 2021,Sarve AR et al., 202, Joanne et al., 2011). MDADI is a reliable and validated self-administered questionnaire pertaining to swallowing related difficulties experienced by the patients following RT. It consist of a global score which consisted single question which provides the information of overall assessment of QOL that is affected due to dysphagia and a composite score which included questions representing emotional, functional and physical response to dysphagia(Chen et al., 2001).

UW-QOL questionnaire is a simple yet clinically relevant measure suitable for assessing the patient's overall QOL including physical and mental health (Rogers et al., 2002). Water Swallow Test (100ml) is a reliable and valid bedside tool to assess swallowing capacity as a quantitative indicator of dysphagia by calculating the parameters viz., the swallowing volume (amount of ml per swallow), the swallowing capacity (the amount of ml per second) and the swallowing speed (the time per swallow). Vermaire et al., 2021 concluded in their study that WST is a good to excellent reliability test for patients with HNC using the parameters, number of swallows, duration, swallowing volume, swallowing capacity, and swallowing speed.

Therefore the aim of Dysphagia/Aspiration at risk structures (DARS) study is to determine whether reducing dose to the pharyngeal constrictors and larynx with dysphagia optimized intensity modulated radiotherapy (Do-IMRT) will lead to an improvement in long term swallowing function and quality of life (QOL) compared to standard IMRT (SIMRT) where dose to DARS were not constrained in HNC patients treated by concurrent chemoradiation

## Materials and Methods

This study was carried out in the Radiotherapy Department, King George's Medical University, Lucknow India. Study includes newly diagnosed, biopsy proven, locally advanced stage II-IV (AJCC Cancer staging Manual, 8th edition), patients of Head and Neck squamous cell carcinoma (HNSCC), registered in the Radiotherapy Department, King George's Medical University, Lucknow India. Study related informed consent was taken from all the patents. Study was approved by Institutional Ethics Committee, King George's Medical University Reference code X-PGTSC-IIA/P13.

A total of 50 patients were prospectively enrolled in the study of which 25 patients were randomized by computer generated random allocation method in each arm of Do-IMRT and SIMRT wherein additional dose constraints were applied to the DARS structures and dose constraints were exempted to the DARS structures respectively. Concealed randomization was done by using computer generated random number and assessors of the water swallow tests were blinded to all other test results. MDADI and UWQOL (Hindi translated version) and 100ml WST questionnaires were filled by all the patients in both the arms before starting the treatment i.e. baseline evaluation. All the procedures were double blinded to eliminate bias.

All patients underwent CT simulation with proper immobilization techniques after which contouring of normal structures including the DARS i.e. superior, middle and inferior pharyngeal constrictors, cricopharyngeus, glottic, supraglottic larynx and esophageal inlet was done as per recommended guidelines in all the patients. Clinical and radiological findings were used to delineate the primary gross tumor volume and nodal volume (GTV) and high risk clinical target volumes (CTV) to incorporate all high risk regions i.e. CTV66.The low risk nodal CTV included the remaining nodal levels at risks i.e. CTV 54 along with PTV66 and PTV54. A dose of 66 Gy in 30 fractions at 2.2 Gy per fraction was delivered to PTV66 and 54 Gy in 30 fractions at 1.8 Gy per fraction was delivered to PTV54.Following were the dose constraints applied to DARS in Do-IMRT: for superior constrictor, middle constrictor, inferior constrictor muscles Dmean<55 Gy; supraglottic larynx and glottis larynx Dmean<40 Gy; cricopharyngeus and esophagus Dmean<30 Gy after which patients were planned accordingly.

All patients were treated with curative intent IMRT-SIB with radiation delivered over 6 weeks (5fractions per week) with concurrent cisplatin 35-40mg/m2 given in weekly regime to all the patients. 7-9 field plan IMRT was delivered by step and shoot technique by synergy linear accelerator with energy of 6 MV.

Patients were assessed weekly during the period of radiotherapy for the acute toxicity. Treatment response, swallowing function and quality of life were assessed at 1st, 3rd, 6th and 12th month from completion of treatment in the follow up period.

Toxicities were graded according to Common Terminology Criteria for adverse events version 5. Assessment of treatment response was done by Response Evaluation Criteria in Solid Tumors (RECIST). Swallowing function and quality of life were evaluated by MDADI using both global and composite score, UW-QOL questionnaires and 100ml WST in the presence of clinician for quantitative measure of swallowing performance of patients for better reliability and accuracy of results.

*Statistical Analysis*

Continuous data were summarized as Mean ± SE (standard error of the mean) whereas discrete (categorical) in number (no.) and percentage (%).Two independent groups were compared by Student's t test. Two independent groups were also compared by repeated measures two factor (group x period) analysis of variance (Repeated Measures ANOVA) and the significance of mean difference within (intra) and between (inter) the groups was done by Tukey's HSD (honestly significant difference)

post hoc test after ascertaining normality by Shapiro-Wilk's test and homogeneity of variance between groups by Levene's test. Two independent categorical groups were compared by chi-square ($\chi^2$) test. A two-tailed ($\alpha$=2) P< 0.05 was considered statistically significant. Analyses were performed on SPSS software (Windows version 22.0).

## Results

*Patient Characteristics*

The age of patients of S-IMRT and Do-IMRT arms ranged from 28-67 and 29-66 years respectively with mean (± Standard Deviation) 46.92 ± 2.04 and 47.88 ± 2.11 years respectively. The mean age of Do-IMRT group was slightly higher than S-IMRT group. The study population was male predominant (1:11.5 female to male ratio) in both arms. The mean ECOG score was slightly higher in S-IMRT group than Do-IMRT group.

Oral cavity cancers were most common (48%) site of malignancy in the S-IMRT arm whereas oropharyngeal cancers were most common site (52.0%) in DO-IMRT arm. Most patients in S-IMRT arm had Stage IVA disease (32%) whereas most patients in Do-IMRT arm had Stage II disease (36.0%). On comparing, the patient characteristics of two arms were found statistically the same (P> 0.05) i.e. did not differ significantly. In conclusion, patients of two arms were demographically and clinically comparable and hence may not influence the study outcome measures (MDADI, toxicity, UW-QOL, WST) (Table 1).

*Dose delivered to DARS*

Comparing the difference in mean radiation dose delivered to the DARS structures i.e. Superior Constrictor muscle (SC), Middle Constrictor muscle (MC), Inferior Constrictor muscle (IC), Supraglottic Larynx(SGL), glottic larynx (GL), cricopharyngeus (CP) and esophagus(ESO) during treatment of patients in both groups (Figure 1(A, B, C and D)); Student's t test showed significantly (P < 0.01 or P < 0.001) lower doses delivered to DARS structures in Do-IMRT arm as compared to S-IMRT arm. The mean dose delivered to the DARS structures in Do-IMRT arm was 22.6, 10.0, 10.1, 12.1, 11.9 and 20.3% lower respectively as compared to S-IMRT arm (Figure 2F).

*Dysphagia*

*MDADI*

On comparing the difference in mean global and composite scores between the two arms (i.e. inter and intra group), Tukey test showed significantly (P< 0.05 or P< 0.01) different and higher scores of both global and composite in Do-IMRT as compared to S-IMRT at both 6 and 12 months in the post radiotherapy period (Table 2 and Figure 2A and 2B).

*Water Swallow Test*

On comparing the difference in mean WST variables scores ( inter and intra group), Tukey test showed significantly (P< 0.05 or P< 0.001) different and higher scores or improvement in both swallowing volume and swallowing capacity of Do-IMRT as compared to S-IMRT

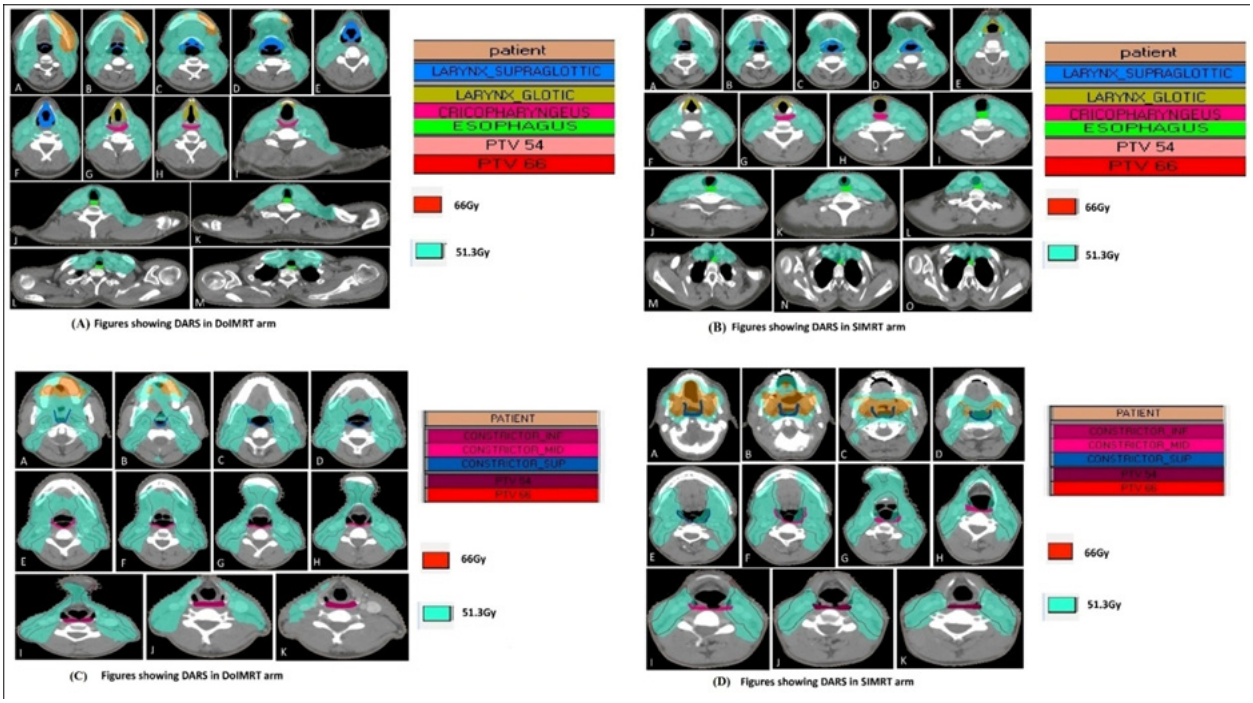


Figure 1. (A) Pictures showing DARS spared in Do-IMRT ARM - Axial CT images of T4bN0M0 Carcinoma Left Retromolar Trigone showing sparing of DARS structures: Supraglottic larynx (A-F), Glottic larynx (G-I) and Esophagus (J-M) (B) Pictures showing DARS not spared in SIMRT ARM - Axial CT images of T4aN0M0 Carcinoma Right Buccal Mucosa showing non-sparing of DARS structures: Supraglottic larynx (A-D), Glottic larynx (E-H) and Esophagus (I-O) (C) Pictures showing DARS spared in Do-IMRT ARM - Axial CT images of T4aN0M0 Carcinoma Hard Palate showing sparing of DARS structures: Superior Constrictor (A-D), Middle Constrictor (E-H) and Inferior Constrictor muscles (I-K) (D) Pictures showing DARS not spared in SIMRT ARM - Axial CT images of T4aN0M0 Carcinoma Hard Palate showing non-sparing of DARS structures: Superior Constrictor (A-E), Middle Constrictor (F-I) and Inferior Constrictor muscles (J-K).

Table 1. Patient Characteristics of Two Arms

| Variable | S-IMRT (n=25) (%) | Do-IMRT (n=25) (%) | t/$\chi^2$ value | P value |
|---|---|---|---|---|
| Age (yrs) | 46.92 ± 2.04 | 47.88 ± 2.11 | 0.33 | 0.745 |
| Sex | | | | |
| Female | 2 (8.0) | 2 (8.0) | 0 | 1 |
| Male | 23 (92.0) | 23 (92.0) | | |
| ECOG (score) | 80.40 ± 1.58 | 79.20 ± 1.40 | 0.57 | 0.573 |
| Diagnosis site | | | | |
| CA larynx | 2 (8.0) | 1 (4.0) | 0.54 | 0.762 |
| CA oral cavity | 12 (48.0) | 11 (44.0) | | |
| CA oropharynx | 11 (44.0) | 13 (52.0) | | |
| T stage | | | | |
| T1 | 2 (8.0) | 3 (12.0) | 2.4 | 0.792 |
| T1a | 1 (4.0) | 0 (0.0) | | |
| T2 | 10 (40.0) | 9 (36.0) | | |
| T3 | 2 (8.0) | 4 (16.0) | | |
| T4a | 7 (28.0) | 5 (20.0) | | |
| T4b | 3 (12.0) | 4 (16.0) | | |
| N stage | | | | |
| N0 | 13 (52.0) | 16 (64.0) | 4.37 | 0.498 |
| N1 | 9 (36.0) | 8 (32.0) | | |
| N2 | 0 (0.0) | 1 (4.0) | | |
| N2a | 1 (4.0) | 0 (0.0) | | |
| N2b | 1 (4.0) | 0 (0.0) | | |
| N2c | 1 (4.0) | 0 (0.0) | | |
| M stage | | | | |
| M0 | 25 (100.0) | 25 (100.0) | 0 | 1 |
| Composite stage | | | | |
| I | 2 (8.0) | 3 (12.0) | 1.38 | 0.848 |
| II | 7 (28.0) | 9 (36.0) | | |
| III | 5 (20.0) | 3 (12.0) | | |
| IVA | 8 (32.0) | 6 (24.0) | | |
| IVB | 3 (12.0) | 4 (16.0) | | |
| Co morbidity: | | | | |
| Nil | 21 (84.0) | 21 (84.0) | 5 | 0.416 |
| Anxiety disorder | 0 (0.0) | 1 (4.0) | | |
| Diabetes mellitus | 0 (0.0) | 1 (4.0) | | |
| History of Tuberculosis | 1 (4.0) | 0 (0.0) | | |
| Hypertension | 3 (12.0) | 1 (4.0) | | |
| Hearing loss | 0 (0.0) | 1 (4.0) | | |

The age, ECOG score and duration of addition of two arms were summarised in Mean ± SE and compared by Student t test (t value) whereas sex, diagnosis site, T stage, N stage, M stage, composite stage, and co morbidity were summarised in number (no) and percentage (%) and compared by $\chi^2$ test ($\chi^2$ value).

at either of the post periods. (Table 3 and Figure 2C, 2D and 2E).

*Quality Of Life*

*Acute Toxicity*

Patients in both arms developed RTOG Grade 1 and 2 skin and mucosal toxicities. Grade 3 mucosal toxicity was seen in 1 patient of Do-IMRT arm. No other patient developed Grade 3 or higher skin/mucosal toxicity. There was no significant difference in incidence of acute skin/mucosal toxicity reactions in patients of both arms.

Table 2. MD Anderson Dysphagia Inventory (MDADI) Scores of Two arms Over the Periods

| MDADI | S-IMRT (n=25) | Do-IMRT (n=25) | Mean difference | P value |
|---|---|---|---|---|
| Global score | | | | |
| Baseline | 2.44 ± 0.16 | 2.08 ± 0.17 | 0.36 | 0.758 |
| 1 month | 2.56 ± 0.16ns | 2.96 ± 0.16*** | 0.4 | 0.627 |
| 3 month | 2.96 ± 0.17* | 3.60 ± 0.13*** | 0.64 | 0.054 |
| 6 month | 3.32 ± 0.14*** | 4.12 ± 0.12*** | 0.8 | 0.004 |
| 12 month | 3.76 ± 0.10*** | 4.56 ± 0.10*** | 0.8 | 0.004 |
| Composite score | | | | |
| Baseline | 58.50 ± 1.96 | 57.51 ± 1.91 | 0.99 | 1 |
| 1 month | 62.62 ± 2.03ns | 69.04 ± 2.04*** | 6.42 | 0.276 |
| 3 month | 70.46 ± 1.71*** | 78.20 ± 1.95*** | 7.74 | 0.089 |
| 6 month | 76.49 ± 1.79*** | 85.52 ± 1.84*** | 9.03 | 0.022 |
| 12 month | 82.44 ± 1.49*** | 92.36 ± 1.17*** | 9.92 | 0.007 |

The MDADI scores of two arms over the periods were summarised in Mean ± SE and compared by RM ANOVA followed by Tukey HSD post hoc test. Intra arms comparisons with respect to baseline-$^{ns}$P > 0.05, *P < 0.05, ***P < 0.001.

*UW-QOL*

On comparing the difference in mean UW-QOL variables scores (inter and intra group), Tukey test showed significantly (P< 0.05 or P< 0.01) different and higher scores or improvement in activity, swallowing, chewing, speech and saliva of Do-IMRT as compared to S-IMRT at either of the post periods (Table 4 and Figure 3A, 3B, 3C, 3D and 3E).

## Discussion

Post radiation complications of dysphagia, aspiration

Table 3. WST Scores of Two Arms Over the Periods

| WST | S-IMRT (n=25) | Do-IMRT (n=25) | Mean difference | P value |
|---|---|---|---|---|
| Swallowing volume (ml/swallow): | | | | |
| Baseline | 14.52 ± 0.60 | 15.48 ± 0.71 | 0.96 | 0.987 |
| 1 month | 12.80 ± 0.57$^{ns}$ | 15.52 ± 0.67$^{ns}$ | 2.72 | 0.072 |
| 3 month | 13.60 ± 0.50$^{ns}$ | 16.48 ± 0.60$^{ns}$ | 2.88 | 0.042 |
| 6 month | 14.88 ± 0.52$^{ns}$ | 17.28 ± 0.64$^{ns}$ | 2.4 | 0.18 |
| 12 month | 16.08 ± 0.59$^{ns}$ | 18.88 ± 0.85*** | 2.8 | 0.055 |
| Swallowing capacity (ml/sec): | | | | |
| Baseline | 12.80 ± 0.97 | 13.40 ± 1.08 | 0.6 | 1 |
| 1 month | 10.00 ± 0.24$^{ns}$ | 11.44 ± 0.65$^{ns}$ | 1.44 | 0.952 |
| 3 month | 12.20 ± 0.50$^{ns}$ | 14.04 ± 0.82$^{ns}$ | 1.84 | 0.812 |
| 6 month | 13.84 ± 0.71$^{ns}$ | 19.28 ± 0.82*** | 5.44 | < 0.001 |
| 12 month | 17.04 ± 0.69*** | 23.40 ± 0.95*** | 6.36 | < 0.001 |
| Time per swallow (sec): | | | | |
| Baseline | 8.44 ± 0.41 | 8.60 ± 0.67 | 0.16 | 1 |
| 1 month | 10.12 ± 0.19* | 9.56 ± 0.45$^{ns}$ | 0.56 | 0.993 |
| 3 month | 8.48 ± 0.29$^{ns}$ | 7.80 ± 0.41$^{ns}$ | 0.68 | 0.973 |
| 6 month | 7.52 ± 0.34$^{ns}$ | 5.72 ± 0.39*** | 1.8 | 0.05 |
| 12 month | 6.12 ± 0.25*** | 4.80 ± 0.42*** | 1.32 | 0.377 |

The WST scores of two arms over the periods were summarised in Mean ± SE and compared by RM ANOVA followed by Tukey HSD post hoc test. Intra arms comparisons with respect to baseline-$^{ns}$P > 0.05, *P < 0.05, ***P < 0.001.

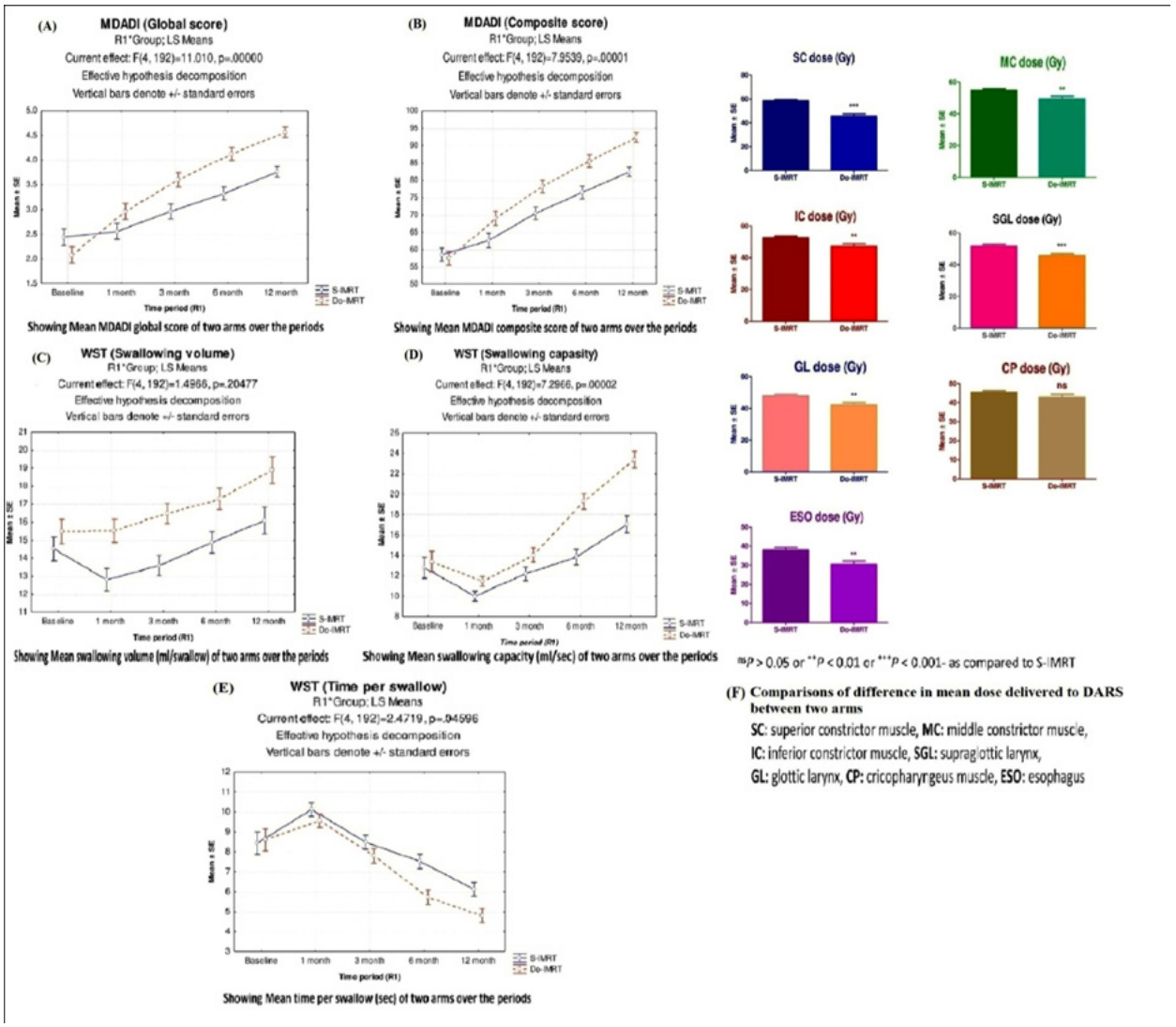


Figure 2. MD Anderson Dysphagia Inventory (MDADI) Global and Composite Score, Mean Dose delivered to DARS between two arms and Water Swallowing Test (WST): (A) Showing Mean MDADI Global score of two arms over the period (B) Showing Mean MDADI Composite score of two arms over the periods (C) Showing Mean swallowing volume (ml/swallow) of two arms over the periods (D) Showing Mean swallowing capacity (ml/sec) of two arms over the periods. (E) Showing Mean time per swallow (sec) of two arms over the periods (F) Comparisons of difference in mean dose delivered to DARS between two arms.

and subsequent pneumonia have emerged as critical radiation related toxicities which negatively impact QOL and really matters in each and every patient of HNC treated by CRT. Although various studies have documented association of radiation dose received by the pharyngeal constrictors, supraglottic larynx, epiglottis, vocal cords, soft palate, esophageal inlet with post radiation complication of dysphagia and aspiration, yet Do-IMRT has not been incorporated in the routine radiation therapeutic procedures in HNC patients. This may be because of lack substantial data assessing dosimetric constraints to DARS structures predictive of post radiation swallowing outcome, identification of DARS structures, dysphagia measurement and clinical factors in the patients of head neck cancer undergoing chemoradiation.

Eisbruch et al., (2004) explored the role of IMRT in sparing the DARS and compared the 3D-CRT technique with two IMRT techniques i.e. S-IMRT and Do-IMRT. They found that the doses of different PTVs were similar with both techniques. The volumes of DARS like pharyngeal constrictors, glottic and supraglottic larynx receiving a dose of more than 50 Gywere reduced more by Do-IMRT compared to S-IMRT.

Laan a et al., (2012) found that, Do-IMRT resulted in better sparing of swallowing organs at risk (SWOARs) compared to S-IMRT. The mean dose in the SWOARs and normal tissue complication probability (NTCP) values for swallowing dysfunction were found to be lower with S-IMRT. The probability of physician-rated RTOG grade 2–4 swallowing dysfunction was reduced with Do-IMRT from 42% to 33%. Difficulties with swallowing solid and liquid foods were lower with Do-IMRT keeping the PTV coverage intact and the doses to OARs lower. Few investigators have studied the capability of IMRT in sparing the swallowing organs at risk (Eisbruch et al., 2004; Fua et al., 2007; Eisbruch et al., 2011). However, in their studies; reduced PTV coverage was obtained in an effort to reduce the dose to SWOARS like supraglottic/

Table 4. UW-QOL Scores of Two Arms Over the Periods

| UW-QOL | S-IMRT (n=25) | Do-IMRT (n=25) | Mean difference | P value |
|---|---|---|---|---|
| Pain | | | | |
| Baseline | 50.00 ± 4.08 | 49.00 ± 3.95 | 1 | 1 |
| 1 month | 48.00 ± 3.51$^{ns}$ | 54.00 ± 4.00$^{ns}$ | 6 | 0.942 |
| 3 month | 59.00 ± 3.19$^{ns}$ | 72.00 ± 1.66*** | 13 | 0.099 |
| 6 month | 66.00 ± 3.19*** | 79.00 ± 1.87*** | 13 | 0.099 |
| 12 month | 76.00 ± 2.27*** | 89.00 ± 2.53*** | 13 | 0.099 |
| Appearance | | | | |
| Baseline | 67.00 ± 4.73 | 68.00 ± 4.45 | 1 | 1 |
| 1 month | 59.00 ± 3.79$^{ns}$ | 64.00 ± 2.92$^{ns}$ | 5 | 0.979 |
| 3 month | 73.00 ± 2.47$^{ns}$ | 77.00 ± 2.00$^{ns}$ | 4 | 0.996 |
| 6 month | 80.00 ± 2.50** | 90.00 ± 2.50*** | 10 | 0.386 |
| 12 month | 96.00 ± 2.36*** | 99.00 ± 1.00*** | 3 | 1 |
| Activity | | | | |
| Baseline | 63.00 ± 4.36 | 65.00 ± 3.23 | 2 | 1 |
| 1 month | 49.00 ± 3.67** | 64.00 ± 3.56$^{ns}$ | 15 | 0.028 |
| 3 month | 65.00 ± 2.50$^{ns}$ | 78.00 ± 2.63* | 13 | 0.105 |
| 6 month | 80.00 ± 3.82*** | 83.00 ± 2.38*** | 3 | 1 |
| 12 month | 89.00 ± 2.92*** | 97.00 ± 1.66*** | 8 | 0.744 |
| Recreation | | | | |
| Baseline | 63.00 ± 4.36 | 63.00 ± 3.57 | 0 | 1 |
| 1 month | 56.00 ± 2.99$^{ns}$ | 69.00 ± 2.18$^{ns}$ | 13 | 0.084 |
| 3 month | 76.00 ± 2.69** | 78.00 ± 3.00*** | 2 | 1 |
| 6 month | 88.00 ± 3.57*** | 85.00 ± 3.23*** | 3 | 1 |
| 12 month | 97.00 ± 2.20*** | 93.00 ± 2.29*** | 4 | 0.996 |
| Swallowing | | | | |
| Baseline | 53.60 ± 4.43 | 52.00 ± 5.72 | 1.6 | 1 |
| 1 month | 39.60 ± 3.49$^{ns}$ | 62.00 ± 3.27$^{ns}$ | 22.4 | < 0.001 |
| 3 month | 55.60 ± 3.92$^{ns}$ | 72.40 ± 1.66*** | 16.8 | 0.015 |
| 6 month | 71.20 ± 1.20** | 78.40 ± 2.75*** | 7.2 | 0.888 |
| 12 month | 76.00 ± 2.45*** | 95.20 ± 2.24*** | 19.2 | 0.002 |
| Chewing | | | | |
| Baseline | 54.00 ± 5.72 | 54.00 ± 4.00 | 0 | 1 |
| 1 month | 48.00 ± 2.00$^{ns}$ | 58.00 ± 3.74$^{ns}$ | 10 | 0.774 |
| 3 month | 52.00 ± 3.51$^{ns}$ | 78.00 ± 5.07*** | 26 | < 0.001 |
| 6 month | 68.00 ± 4.90$^{ns}$ | 88.00 ± 4.36*** | 20 | 0.018 |
| 12 month | 92.00 ± 3.74*** | 98.00 ± 2.00*** | 6 | 0.99 |
| Speech | | | | |
| Baseline | 69.20 ± 4.72 | 72.40 ± 4.09 | 3.2 | 0.999 |
| 1 month | 62.00 ± 3.27$^{ns}$ | 80.80 ± 2.94$^{ns}$ | 18.8 | 0.001 |
| 3 month | 73.20 ± 2.87$^{ns}$ | 86.80 ± 3.04** | 13.6 | 0.073 |
| 6 month | 89.20 ± 2.94*** | 89.20 ± 2.94*** | 0 | 1 |
| 12 month | 94.00 ± 2.45*** | 98.80 ± 1.20*** | 4.8 | 0.988 |
| Shoulder | | | | |
| Baseline | 90.40 ± 2.86 | 90.00 ± 3.61 | 0.4 | 1 |
| 1 month | 75.60 ± 3.22*** | 81.60 ± 3.68$^{ns}$ | 6 | 0.911 |
| 3 month | 88.00 ± 3.00$^{ns}$ | 90.40 ± 2.86$^{ns}$ | 2.4 | 1 |
| 6 month | 94.80 ± 3.17$^{ns}$ | 97.60 ± 1.66$^{ns}$ | 2.8 | 1 |
| 12 month | 96.00 ± 3.00$^{ns}$ | 98.80 ± 1.20$^{ns}$ | 2.8 | 1 |
| Taste | | | | |
| Baseline | 74.80 ± 4.36 | 72.80 ± 3.54 | 2 | 1 |
| 1 month | 53.20 ± 4.82*** | 43.60 ± 4.69*** | 9.6 | 0.735 |
| 3 month | 58.00 ± 4.58** | 58.80 ± 3.67* | 0.8 | 1 |
| 6 month | 68.00 ± 2.58$^{ns}$ | 70.80 ± 2.37$^{ns}$ | 2.8 | 1 |
| 12 month | 75.60 ± 3.22$^{ns}$ | 79.60 ± 2.86$^{ns}$ | 4 | 0.999 |
| Saliva | | | | |
| Baseline | 76.80 ± 3.35 | 75.60 ± 3.22 | 1.2 | 1 |
| 1 month | 39.60 ± 3.49*** | 58.80 ± 3.67*** | 19.2 | < 0.001 |
| 3 month | 54.00 ± 4.00*** | 71.20 ± 1.20$^{ns}$ | 17.2 | 0.001 |
| 6 month | 66.80 ± 2.22$^{ns}$ | 77.20 ± 2.62$^{ns}$ | 10.4 | 0.264 |
| 12 month | 71.20 ± 1.20$^{ns}$ | 90.40 ± 2.86** | 19.2 | < 0.001 |
| Mood | | | | |
| Baseline | 51.00 ± 4.67 | 51.80 ± 4.73 | 0.8 | 1 |
| 1 month | 50.00 ± 3.82$^{ns}$ | 53.00 ± 2.63$^{ns}$ | 3 | 1 |
| 3 month | 65.00 ± 2.89* | 61.00 ± 2.53$^{ns}$ | 4 | 0.997 |
| 6 month | 66.00 ± 2.45* | 72.60 ± 2.86*** | 6.6 | 0.918 |
| 12 month | 79.00 ± 2.36*** | 85.00 ± 2.50*** | 6 | 0.954 |
| Anxiety | | | | |
| Baseline | 53.20 ± 4.82 | 52.40 ± 4.05 | 0.8 | 1 |
| 1 month | 54.40 ± 4.40$^{ns}$ | 55.60 ± 3.92$^{ns}$ | 1.2 | 1 |
| 3 month | 67.60 ± 3.28* | 72.00 ± 2.65*** | 4.4 | 0.997 |
| 6 month | 74.40 ± 3.06*** | 73.60 ± 1.99*** | 0.8 | 1 |
| 12 month | 90.40 ± 2.86*** | 88.00 ± 3.00*** | 2.4 | 1 |

The UW-QOL scores of two arms over the periods were summarised in Mean ± SE and compared by RM ANOVA followed by Tukey HSD post hoc test. Intra arms comparisons with respect to baseline- $^{ns}$P > 0.05, *P < 0.05, ***P < 0.001.

glottic larynx and PCM.

Laan et al., (2013) demonstrated that the benefits of Do-IMRT depended on several factors like skills of the planner, the time taken for treatment planning, the decision of a clinician to accept a moderate compromise in the PTV coverage with an aim to spare the DARS better and the specific treatment optimization methods. They explained that the tumor site and the target volume influenced the reduction in NTCP. Do-IMRT was more effective in cases where the target and DARS overlapped partially as compared to the cases where there was a complete overlap. Incorporation of these factors into the clinical practice in their study showed an increased benefit with Do-IMRT.

Caudell et al., (2010) compared two different methods, whole-field IMRT (WF-IMRT) and dynamic supraclavicular field (D-SCLV) technique to spare the swallowing-related structures like the larynx and, inferior pharyngeal constrictor (IPC) in head and neck cancer. The PTV coverage was found to be similar with both methods; however, the dose to swallowing-related structures (larynx and IPC) was reduced significantly with the D-SCLV plans.

Webster et al., (2008) studied the impact of WF-IMRT on target coverage and laryngeal sparing and compared it with Junctioned-IMRT (J-IMRT). Their results showed that WF-IMRT was better in laryngeal sparing as a significant reduction was obtained in the mean larynx dose as compared to the J-IMRT. The results of the DARS trial conducted by Nutting et al., (2020) showed that doses of superior pharyngeal constrictor muscle (PCM), Inferior PCM and Middle PCM were reduced with Do-IMRT. Do-IMRT had significantly higher MDADI scores and showed improved swallowing function and quality of life

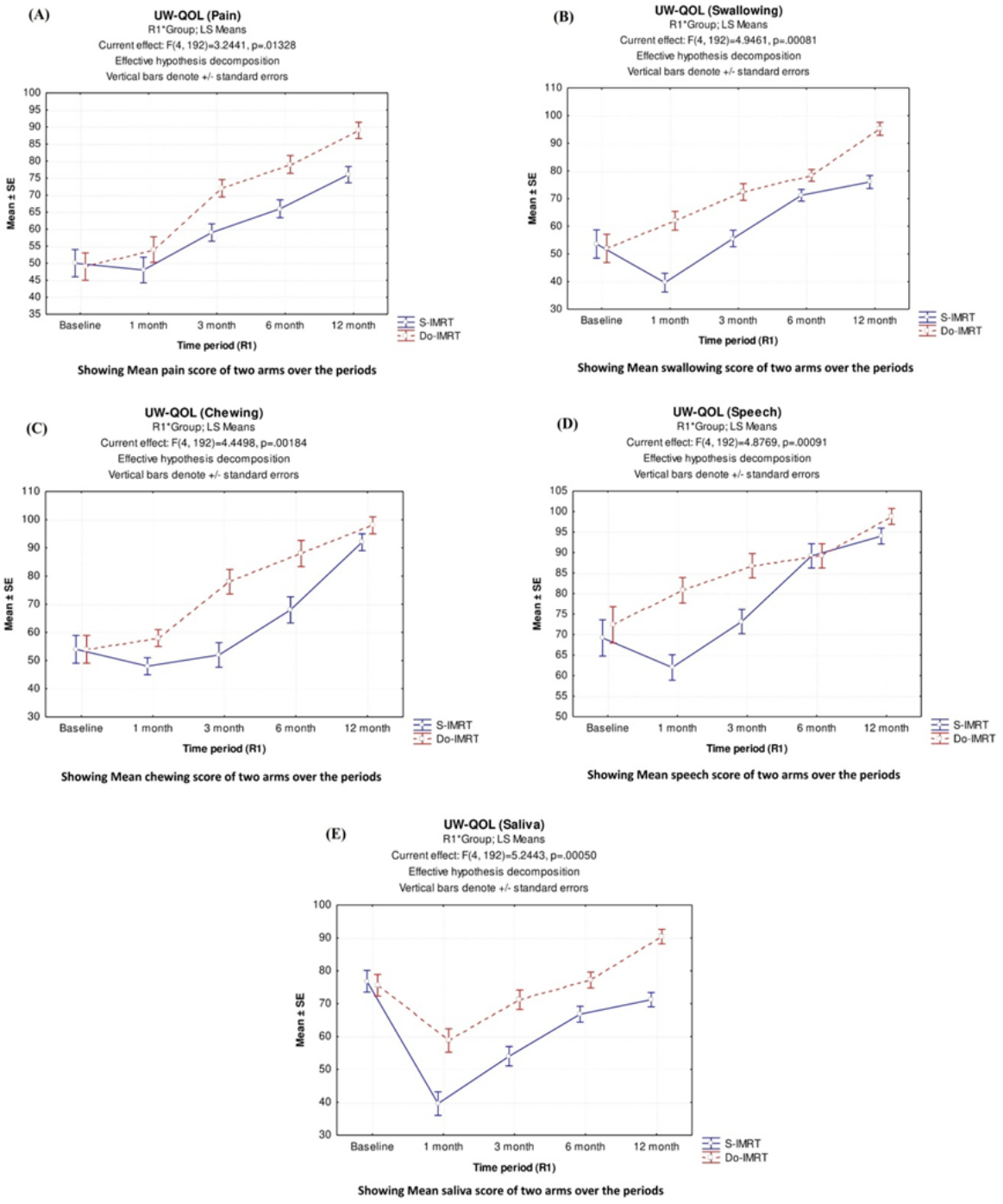


Figure 3. University of Washington-Quality of Life (UW-QOL) Showing: (A) Mean pain score of two arms over the periods (B) Mean swallowing score of two arms over the periods (C) Mean chewing score of two arms over the periods (D) Mean speech score of two arms over the periods (E) Mean saliva score of two arms over the periods.

as compared to SIMRT.

Schwartz et al., (2010) calculated Oropharyngeal Swallowing Efficiency (OPSE) scores in oropharyngeal cancer patients to study swallowing efficiency and found a significant correlation between doses delivered to superior and middle pharyngeal constrictor muscles and OPSE scores indicating dysphagia. Similarly in our study, we have found that there was significant increase in MDADI global (19.3%) and mean composite score (8.7%) in Do-IMRT arm patients as compared to SIMRT arm patients. Furthermore, on applying dose constraints to Do-IMRT arm patients, the dose delivered to DARS was lower as compared to S-IMRT arm patients and subsequently resulted in significant improvement in swallowing outcome in terms of swallowing, chewing, speech. In conclusion, patients undergoing Do-IMRT have improved swallowing functions post radiotherapy compared to patients undergoing S-IMRT.

Although dose escalation with IMRT may improve tumor control which is a surrogate for overall survival, IMRT prerequisites robust reproducibility and quality assurance. We need to know for sure what to target and what could be avoided safely as well as normal tissue constraints. Periodic portal imaging should be performed

to quantify end to end uncertainties in treatment delivery chain to determine PTV margins. Stringent patient selection criteria should be put in place so as not to compromise PTV coverage while sparing OARs as otherwise treatment by IMRT would be futile.

## Author Contribution Statement

The authors confirm contribution to the paper as follow: study conception and design: SG, MLBB, RG; data collection; SG, SB, AG IJG, DJ, SS, NS, MLBB, RG; analysis and interpretation of results: SG, VVB, MPSN; draft manuscript preparation: SG, SB, MLBB. All authors reviewed the results and approved the final version of the manuscript.

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*Ethical Declaration*

How the ethical issue was handled (name the ethical committee that approved the research) - Institutional Ethics Review Board, King George's Medical University, Lucknow.

*Conflict of Interest*

NIL.

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