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Original research article

Dose to swallowing structures and dysphagia in head and neck Intensity Modulated Radiation Therapy A long term prospective analysis

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ABSTRACT

Aim: To analyse the long term swallowing function in head and neck cancer patients and correlate with the dose to midline swallowing structures.

Background: The use of concurrent chemo radiation (CRT) as the present standard of care resulted in high rates of early and late toxicities. Dysphagia, aspiration, and xerostomia are early as well as late effects of radiation. Not many studies on the dysphagia scores during radiation and follow-up period have correlated with dose to the swallowing structures, hence this study.

Materials and Methods: Histologically proven head and neck cancer patients treated with intensity modulated radiation therapy were accrued in this study. The pharyngeal constrictors, larynx and cervical oesophagus were contoured and labelled as midline swallowing structures. The volume of the midline swallowing structures which were outside the Planning target volume (PTV) was delineated separately and was given a mean dose constraint of 45 Gy. Dysphagia was assessed at baseline, weekly during irradiation and up to six years. The dose to the structures for swallowing was correlated with degree of dysphagia.

Results: There was a gradual increase in the dysphagia grade during the course of radiation. There was significant recovery of late dysphagia compared to dysphagia during the completion of radiation therapy in patients who received <45 Gy to the swallowing structures ($p < 0.0001$).

Conclusion: Giving a constraint to the swallowing structures and limiting it to <45 Gy resulted in earlier recovery of swallowing function resulted leading to good physical, mental and social well being of the patients when compared to those who received >45 Gy.

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1. Background

Head and neck cancer (HNC) is the sixth most common cancer worldwide, accounting for about 3.2% of all malignancies.[1] In India, it accounts for 23% of all cancers in men and 9% in women.[2] Radiotherapy has a major role in the treatment of HNC owing to a complicated anatomic relationship between the tumour and the normal structures in maintaining the quality of life (QOL) of the patient. The use of concurrent chemo radiation (CRT) as the present standard of care resulted in a 19% reduction in the risk of death and an overall 8% improvement in five year survival compared with radiotherapy alone but with high rates of early and late mucosal and pharyngeal toxicities.[3] Dysphagia, aspiration, and xerostomia are important early as well as late effects of radiation therapy that have significant QOL and resource implications after treatment. Several authors have looked at the relationship of treatment-related toxicities and QOL for HNC patients considering xerostomia to be the primary determinant of long term toxicity in survivors. Langendijk et al. reported that dysphagia was the strongest determinant of overall QOL following 3D conformal radiation therapy.[4] In a prior institutional study, 38.5% of patients with loco regionally advanced HNC treated with definitive CRT with increasing age had composite dysphagia.[5] Swallowing dysfunction compromises QOL and is found to be associated with anxiety, depression, isolation and loss of social relationships.[6] The advanced techniques of radiation are mainly aimed at improving toxicity profile and, thereby, QOL. With the advent of intensity modulated radiation therapy (IMRT), the structures responsible for swallowing function can be spared without compromising the target volume coverage.

2. Aim

The aim of this study is to correlate the dose received by the midline swallowing structures by sparing it by the IMRT technique and the grade of dysphagia at baseline, during treatment and follow-up up to maximum six years following definitive and adjuvant radiation therapy with or without concurrent chemotherapy.

3. Materials and methods

This prospective study was conducted on 30 histologically proven HNC patients undergoing IMRT, either radical or adjuvant with or without concurrent chemotherapy between October 2012 and March 2014, following ethical clearance and informed consent. The baseline dysphagia score prior to starting radiation was recorded based on the RTOG criteria. All the patients were immobilized using an aquaplast cast with appropriate head rest. Contrast enhanced planning computerized tomography (CT) images of 3 mm slice thickness were acquired from the vertex to carina.

The gross tumour volume (GTV) was delineated taking into account the clinical examination, videolaryngoscopy/direct laryngoscopy findings and CT scan. The clinical target volume (CTV) and planning target volume (PTV) were created according to institutional guidelines. Along with the other organs at risk in HNC, with regards to the swallowing apparatus, the following anatomical structures were identified and delineated: the constrictor muscles (Fig. 1), the larynx (Fig. 2) and the oesophagus (Fig. 3). The oesophagus was contoured with its caudal-most extent 2 cm below the caudal-most extent of the target volume in the head and neck.

The components of the above swallowing apparatus were united and labelled as midline swallowing structure. The parts of the midline swallowing structure which were outside the PTV were delineated and labelled separately as <45 Gy

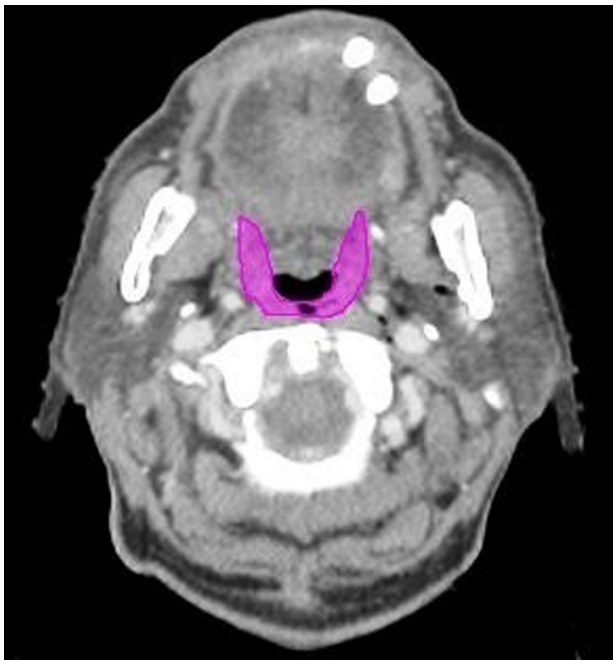

Fig. 1 – Contouring of constrictor muscle.

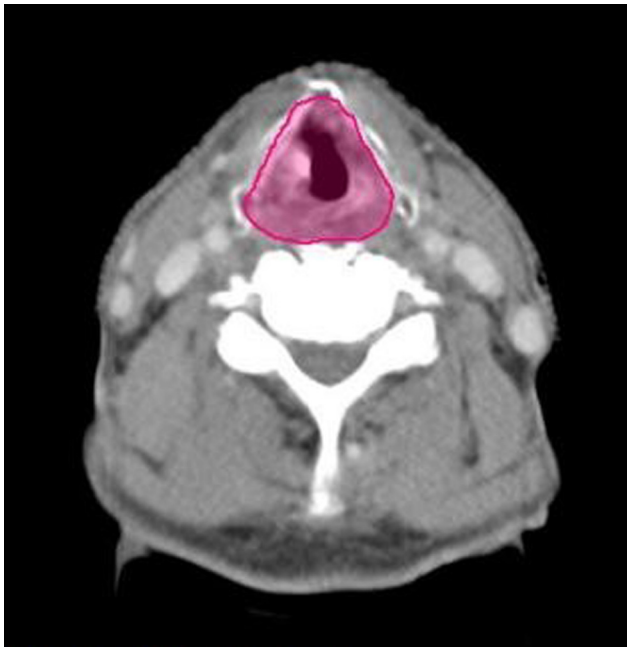

Fig. 2 – Contouring of larynx.

Fig. 3 – Contouring of oesophagus.

constraint swallowing structure and mean dose constraint of <45 Gy was given, although it was not a strict criterion to achieve it. The swallowing structure which was within the PTV was irradiated with no attempt to spare or reduce the dose. IMRT treatment technique was planned using the Prowess version 4.7 and Oncentra treatment planning system. Concurrent weekly Cisplatin chemotherapy was administered wherever indicated. The mean dose to the <45 Gy constraint swallowing structure was assessed using dose volume histogram (DVH). Dysphagia was assessed at baseline, regular weekly intervals during the course of radiation and six weeks after completion of treatment and follow-up for up to maximum six years using RTOG criteria. The dose to the <45 Gy constraint swallowing structure was correlated with the degree of dysphagia.

3.1. *Statistics*

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on mean ± SD (Min- Max) and results on categorical measurements are presented in Number (%). Significance is assessed at the 5% level. The statistical software. namely SAS 9.2, SPSS 15.0, stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment version 2.11.1 were used for the analysis of the data and Microsoft word and excel have been used to generate the graph and tables. Fishers exact test was used to analyse the results.

4. Results

The patient characteristics are shown in Table 1. The mean age was 57 years with majority of the primary (36.7%) being oral cavity tumours followed by oropharynx (30%). Squamous cell carcinoma was the most common histology. Eight patients (27%) had history for alcohol consumption, 13 (43%) were smokers and 8 (27%) patients were tobacco chewers. Fourteen (47%) underwent surgery followed by adjuvant radiation and 16 (53%) patients received at least one cycle of concurrent chemotherapy.

Table 1 – Patient characteristics and frequency (%).

Gender	
Male	19 (63)
Female	11 (37)
Age	
<50yrs	5 (16)
50 60 yrs	14 (46)
>60 yrs	11 (36)
Primary site	
Oral cavity	11 (36.7)
Oropharynx	9 (30)
Laryngopharynx	3 (10)
Nasopharynx	3 (10)
MUO	1 (3)
Parotid	3 (10)
Tumour classification	
Tx	5 (16.6)
T_1	5 (16.6)
T_2	10 (33.3)
T_3	8 (26.6)
T_4	2 (6.6)
Node classification	
N0	16 (53.3)
N1	6 (20)
N2a	4 (13.3)
N2b	2 (6.6)
N2c	1 (3.3)
N3	1 (3.3)
Stage	
I	5 (17)
II	9 (30)
III	7 (23)
IV	9 (30)

4.1. *Correlation of the dose to swallowing structure and dysphagia*

The <45 Gy constraint to swallowing structures was achieved in 13 (43.3%) patients. The mean dose was in the range of 4550 Gy in five patients (16.6%) and was >50 Gy in 12 patients (40%).

The subjective assessment of dysphagia was done using RTOG criteria at baseline i.e., before starting CRT, weekly during the course of radiation, at 6 weeks following completion and during follow up for minimum of four years and maximum six years. Comparison of weekly dysphagia grades during the course of radiation between the groups of patients receiving <45 Gy, 4550 Gy and >50 Gy mean dose to <45 Gy constraint volume showed no statistical difference. The baseline grade of dysphagia in all the three groups was 0.47 ± 0.63. There was a gradual weekly increase in grade subsequently in all the three groups increasing from 0.7 ± 0.65 to 2.2 ± 0.57 at week 6 of radiation. However, there was no statistically significant difference between the three groups with a mean p value of 0.48. Dysphagia assessment at six weeks post radiation therapy was done, five (16.7%) patients had grade two dysphagia and one

Table 2 – Comparison between dysphagia at 6 weeks post RT with dysphagia during the last week of radiation.

	<45 Gy	Mean dose to DARS 4550 Gy	>50 Gy
Dysphagia grade during the last week of radiation	2.09 ± 0.54	2.40 ± 0.55	2.25 ± 0.62
Dysphagia Grade at 6 weeks post RT	0.54 ± 0.52	0.60 ± 0.89	1.08 ± 1.08
p value	0.00001	0.021	0.004

Table 3 – Results from selected series regarding late toxicity in the head and neck cancer patients treated with radiation therapy.

S. no	Technique	Authors	No. of patients	Median follow up (months)	Chemotherapy %	Stage III/IV (No.)	Grade III/IV toxicity (%)
1	IMRT	De Arruda et al.[17]	50	18	86	92	6
2	IMRT	Lee et al.[18]	41	31	100	100	12
3	IMRT	Studer et al.[19]	115	18	78	52	15
4	3DCRT	Denie et al.[20]	44	60	61	100	68
5	3DCRT	Huguenin et al[20]	224	39	50	97	51
6	IMRT	Our study	30	30	53	16	10

(3.3%) patient had grade three dysphagia. Ten (33.3%) patients had grade one dysphagia; the remaining 14 (46.7%) patients did not exhibit any grade of dysphagia. Comparison of dysphagia at baseline and six weeks post treatment showed no significant increase in dysphagia scores.

Also, our study did not show any increase in post treatment dysphagia between the groups which received <45 Gy, 4550 Gy. Patients who received <45 Gy showed significant reduction in dysphagia at 6 weeks follow up when compared to the scores at completion of radiation (Table 2) P value = 0.00001.

4.2. *Correlation of independent factors to dysphagia*

Apart from radiation dose to the swallowing structure, the impact of factors such as smoking, alcohol, tobacco chewing, site of primary, T stage, N stage, surgery, concurrent chemotherapy and neo-adjuvant chemotherapy on post treatment dysphagia was determined. Among these factors, higher T stage and addition of neo- adjuvant chemotherapy had a significant correlation with dysphagia six weeks post treatment. In a higher T stage, due to a higher tumour burden with increased volume of PTV, more of the swallowing structure was invariably included in the PTV resulting in increased dysphagia scores.

4.3. *Follow up*

Out of the 30 patients, 10 patients expired and 7 patients were lost to follow up, the remaining 13 patients were followed up for maximum six years. The last follow up was in August 2018. Ten patients were disease free and had normal swallowing function and 3 patients were on liquid diet. The mean dose to swallowing structure in these 10 and 3 patients was <45 Gy and >50 Gy respectively. All the patients whose dose to the swallowing structure was <45 Gy had normal swallowing function at 6 year follow-up and those who received >50 Gy had grade III dysphagia which was statistically significant with a p value of 0.003.

5. Discussion

The present prospective study was designed to evaluate the degree of dysphagia in HNC patients receiving radical radiation by the IMRT technique. RTOG questionnaire was used to assess dysphagia. A dose constraint of <45 Gy was prescribed to the midline swallowing structure which was outside the PTV volume and there was no strict criteria to achieve it. No attempt was made to spare the swallowing structures which were close to or within the PTV volume. Our methodology was in accordance with the study done by Eishbruch et al, where the authors used IMRT to reduce dose to the midline swallowing structures without any compromise on the target dose.[7] The authors found a decrease in the incidence of late dysphagia. Majority of the patients in the present study were in the age group 5060 years, with a mean age of 57 years. This is similar to a study done by Amin et al, where the median age was 56 years.[8] Oral cavity (36.7%) was the most common site of primary tumour followed by the oropharynx (30%) in our study group. Caglar et al.[9] and Eishbrush et al.[10] included only laryngeal and oropharyngeal tumors, Peponi et al. included all the head and neck sites similar to that of our study.[11] In our study, <45 Gy constraint was given to the swallowing structure outside the PTV and achieving this dose constraint was not an absolute requirement. A similar study was done by Eishbruch et al.; however. the dose constraint was 50 Gy to the swallowing structure. This was based on the observation that the lowest dose received to most of the constrictors involved in a stricture was 50 Gy.[7] Galloway et al.[12] in a study describing laryngeal irradiation with midline swallowing structure sparing IMRT, a constraint of mean dose 50 Gy was given to the midline swallowing structure. Even in their study, achieving the 50 Gy constraint was not an absolute requirement and had to be compromised when the tumour was close to the pharynx.

Feng et al. found that no aspiration events were observed when the dose to the midline swallowing structure was kept below 45 Gy.[13] Constraint in our study is similar to that done by Peponi et al. where the authors used mean dose constraint of <45 Gy to the midline swallowing structure and included all primary sites in their analysis.[11]

This is the first prospective study where baseline dysphagia scores were recorded and compared with weekly dysphagia during radiation as well as long term follow up. None of the previous studies have compared the effect of midline swallowing structure sparing IMRT during the course of radiation. The weekly dysphagia scores did not differ significantly between the three groups of patients i.e. <45 Gy, 4550 Gy and >50 Gy. However, an important observation was made by Amin et al., namely that a dose to the swallowing structures during IMRT was significantly lower (55.2 Gy) when a constraint was given compared to planning without a dose constraint (62.2 Gy).[8]

In our study only one patient had grade 3 dysphagia (3%) at 6 weeks post radiation. This is in contrast to a study by Forastiere et al.[14] where 23% of the patients receiving radiation were only on liquid diet. The reason probably would be that fifty percent of the patients in their study received altered fractionation. Our patients did not receive altered fractionation. In a similar study by Caglaret et al.[9] 32% of the patients developed clinically significant aspiration and 37% of the patients developed strictures. Caudell et al. on assessing long term dysphagia following definitive radiotherapy of HNC reported that 38.5% of patients had late severe dysphagia.[5] Even higher rates of toxicity were reported by Denis et al., where the authors reported that 68% of patients treated with definitive IMRT without dose constraint to swallowing structure had grade III dysphagia.[15] Peponi et al. reported similar results with a median follow up of fifty-five months and found 9% incidence of grade III/IV toxicity, when swallowing structure sparing IMRT was used.[11] At six years follow up, our study showed 10% incidence of grade III&IV toxicity. Results from selected series regarding late toxicity treated with radiation therapy with or without concurrent chemotherapy are shown in Table 3. In our study, dysphagia at 6 weeks post treatment was compared with baseline dysphagia. No significant increase in dysphagia was seen when post treatment dysphagia scores were compared with pre-treatment baseline scores. This proves the effectiveness of using swallowing structure sparing IMRT in reducing the incidence of dysphagia. Only two previous published studies by Schwartz et al.[16] and Langendijk et al.[4]They have recorded the pre-treatment dysphagia scores. Most of the other studies were retrospective and analysed only late dysphagia scores which have led to over-estimation of dysphagia following radiation. Our study showed a significant improvement in late dysphagia scores when compared with dysphagia scores during the last week of radiation therapy in patients who received <45 Gy to the swallowing structure. This is thought to represent a consequential effect of severe acute depletion of mucosal and sub-mucosal stem cells due to irradiation. Reduction in dose to the swallowing structure might have led to faster recovery of mucosal cells and, in turn, decreased dysphagia scores.

There was no correlation with the use of concurrent chemotherapy and dysphagia scores similar to study done by Schwartz et al.,[16] Forastiere et al.,[14] and Eishbruch et al.[10] have reported increased incidence of late dysphagia with the addition of concurrent chemotherapy. This could be explained as potentiation of action of radiation by concurrent chemotherapy on the swallowing structures. But in those studies, swallowing structure sparing IMRT was not employed. The effect of concurrent chemotherapy with the swallowing structure sparing IMRT has not been studied extensively apart from our study.

The effect of neo-adjuvant chemotherapy on late dysphagia scores has not been correlated in previous studies. In our study, we found a significant correlation between late dysphagia scores and the addition of neoadjuvant chemotherapy to the treatment regimen. In our study, neoadjuvant chemotherapy was given in those patients who had a locally advanced disease. So this might actually be an impact of a higher T stage of the disease, as target volumes in these patients would be considerably large with more volume of the swallowing structure in the PTV. The limitation of our study is that the sample size is small. Also, the impact of salivary function on dysphagia score was not studied. Our study is a subjective study based on patients reported questionnaires and objective assessment of dysphagia with video fluoroscopy or esophagogram was not done.

This is the first prospective study where baseline dysphagia scores were recorded and compared with weekly dysphagia during radiation as well as long term follow-up. None of the previous studies have compared the effect of swallowing structure sparing IMRT during the course of radiation.

6. Conclusion

Giving a constraint to swallowing structure and limiting it to <45 Gy resulted in earlier recovery of swallowing function resulting in good physical, mental and social well being of the patients when compared to those who received >45 Gy.

The dysphagia scores correlated with the dose received by the swallowing structures. No significant increase in post radiation dysphagia was observed when dose to swallowing structures was limited using IMRT. Recovery from dysphagia following completion of radiation correlated with dose to the swallowing structures.

Future studies with a larger sample size may help in establishing the dose response relationship of midline swallowing structures and impact of independent factors on radiation induced dysphagia.

Conflict of interest

None declared.

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