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ORIGINAL RESEARCH ARTICLE

Dose Constraints for Remaining Volume at Risk and its Clinical Significance in IMRT Planning of Head and Neck Cancers

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ABSTRACT

Introduction: Newer radiotherapy techniques like Intensity Modulated Radiotherapy (IMRT) have led to the delivery of precision radiotherapy where lower doses to normal tissues can be achieved which may otherwise cause more acute and chronic radiotherapy induced toxicities. Radiotherapy toxicity acute oral mucositis presents with pain, and difficulty in swallowing, leading to decreased nutrition intake, weight loss, treatment breaks and ultimately poor outcomes. To reduce acute oral mucositis, it should be considered as an organ at risk and dose constraints to be prescribed. ICRU 83 refers to these regions as remaining volume at risk (RVR). The present study evaluates whether acute mucositis can be decreased clinically by delineating RVR in such patients.

Material and Methods: Fifty patients of head and neck cancers presented to the department who were to be treated with definitive concurrent chemoradiotherapy by IMRT were selected. Patients were randomly assigned in a 1:1 ratio into two groups (twenty-five each)- group 1 (RVR dose constraints not prescribed) and group 2 (RVR dose constraints of D_{mean} 30 Gy prescribed). Both groups evaluated and compared the dosimetric parameters of planning target volumes, OARs, and RVR. The radiation toxicities of skin, parotid and RVR were also assessed. The statistical analysis was done using an unpaired t-test and chi-square test.

Results: The median age in both groups was 55 years with male to female ratio 24:1. Dosimetric parameters of PTV, OARs and RVR did not show any statistical difference. No grade IV skin reactions or xerostomia were seen in either group, though the severity of reactions was higher in group 1. During radiotherapy, no grade IV mucositis was seen in group 2, whereas the group had in 12% of patients. After radiotherapy, in a follow-up of one month, grade III mucositis was persistent in all patients of group 1 (44%) in comparison to group 2 where none had grade III mucositis.

Conclusion: The delineation of RVR and prescribing dose constraint decreased the severity of oral mucositis clinically, but a significant difference could not be seen in the dosimetric parameters of RVR.

Keywords: Head neck cancers, Oral mucositis, RVR.

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INTRODUCTION

Radiotherapy is an important modality to treat head and neck cancers. Newer radiotherapy techniques like intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) have led to the practice of precision radiotherapy where the advantage of lower doses to normal tissues can be achieved which may otherwise cause more acute and chronic radiotherapy induced toxicities.

Acute radiotherapy toxicities include primarily oral mucositis, which may present as pain, difficulty swallowing, and sometimes bleeding. These complications further cause a decrease in appetite and intake of nutrition, leading to significant weight loss, treatment breaks and poor outcomes. Other acute reactions may be related to skin toxicity, though it is not seen in severe grades with the advent of newer techniques. The doses to chronic radiotherapy toxicities include xerostomia, dysphagia and skin fibrosis. Xerostomia and dysphagia are major concerns clinically and dose constraints to parotid glands and dysphagia aspiration-related structures may help to reduce these chronic side effects.

Theoretically, to reduce acute mucositis in patients of head and neck cancers undergoing radiotherapy, oral mucosa should be considered as an organ at risk (OAR), needs to be delineated, and dose constraints to be prescribed to this region, so that decreased radiotherapy dose is delivered. ICRU 83 refers to these regions as the remaining volume at risk (RVR). Practically, radiotherapy planning may have challenges to achieve it, if the planning target volumes of tumor are adjacent or overlapping this RVR. The present study evaluates

whether acute mucositis can be decreased clinically by delineating RVR in such patients.

MATERIAL AND METHODS

Fifty consecutive patients of head and neck cancers presented in the Department of Radiation Oncology in R.R Cancer Institute, SRMS, Bareilly treated with definitive concurrent chemoradiotherapy were randomly divided into 2 groups of 25 patients in each group.

Patient Selection

Inclusion criteria

Histologically proved squamous cell carcinoma head and neck cancer malignancies; age ≥18 years; karnofsky performance status>70; normal hemogram, renal and liver function tests

Exclusion criteria

Patients with prior or synchronous malignancy; patients who underwent prior surgery; distant metastasis; previously treated patients with radiotherapy.

Randomization

Patients were randomly assigned in a 1:1 ratio into two groups (25 each) as follows who would be planned for chemoradiation:

Group I- RVR dose constraints not prescribed.

Group II- RVR dose constraints of Dmean 30 Gy prescribed.

Chemotherapy administration

- Patients received cisplatin 35 mg/m^2 weekly.
- Was adequately hydrated with 2 to 2.5 liters of IV fluids and supplemented with intravenous KCL and $MgSo_4$
- Radiotherapy was delivered within one hour of administration of cisplatin.
- Before chemotherapy administration, proper antiemetic therapy with 5-HT3 antagonist, dexamethasone, and ranitidine was given.

Radiotherapy Planning and Technique

Immobilization

All patients were treated in supine position on linear accelerator by IMRT technique. Using a thermoplastic cast, a fixed 5-point mask system was used to immobilize the head, neck and shoulders. The head support was adapted according to the neck position of the patient.

Radiotherapy planning

CECT scan radiotherapy planning (RTP) of 3 mm slice thickness was obtained in supine position with three radio-opaque fiducial markers. Hexaopaque dye was injected during radiotherapy planning.

Image acquisition and registration

These images were then transferred through Digital Imaging and Communications in Medicine (DICOM-CT) into the eclipse treatment planning system (TPS) (Version 13.6, Varian Medical System, Inc, paloAlto, CA, US). After transferring to TPS the CT origin moved to intersection of plane of the fiducial marker. Radiotherapy treatment planning requires accurate patient data such as external body contours and internal anatomy.

Contouring

In 3 mm slice thickness used for delineation of remaining volume at risk (RVR), OAR, CTV and PTV. RVR was contoured according to ICRU 83. In accordance with the radiation therapy oncology group (RTOG 0225) the volumes were:-

- *GTV*: gross disease, including the primary tumor and enlarged lymph nodes as demonstrated on imaging modalities.
- *CTV1:* (clinical target volume): a margin of 1-cm around the GTV will be taken.
- *CTV2*: defined as areas of local-regional failure for nodal region.

Target and OARs delineation

The OARs delineated included left and right parotids, spinal cord, PRV spine, brain stem, brain, eye, lens, optic, chiasma, optic nerve, cochlea (right & left), lips and mandible. Delineation of gross tumor volume, clinical target volume, and planning target volume-GTV: Gross Tumor Volume (GTV) is the gross demonstration of the extent and location of the tumor.it may consist of a primary tumor (primary tumor GTV or GTV-n), metastatic regional nodes(s) (nodal GTV or GTV -n) or distant metastasis (metastatic GTV or GTV -m). GTV encompassing both the primary tumor and the nodes may be delineated as seen in CECT images.

Clinical target volume

The CTV is a volume of tissue that contains a demonstrable GTV and/or subclinical malignant disease with a certain probability of occurrence considered relevant for therapy. The delineation of the CTV is currently based on guidelines of the selection of lymph node target volumes for definitive head and neck radiation therapy by Julian. B, a 2019 update that our department follows.[1]

Planning target volume

A 5 mm PTV margin is taken as per our departmental protocol.

Planning organ at risk volume

margins have to be added to the oars to compensate for these uncertainties and variations which is 5 mm for the spinal cord and 3 mm for brain stem, cochlea and optic chiasma.

OAR

Organ	*Dose constraints*
PRV Spine	$D_{max} \leq 50$
Mandible	Point Dose<70
	1 cc<75
	Dmax<54
Brainstem	D1-10cc ≤ 59
	D_{max}<64 (Point dose<1cc)
	Mean dose <20
Parotid gland (right & left)	Mean dose <25
	Mean dose <26
Cochlea (right & left)	Mean dose ≤45
Lips	D_{mean}<30
Optic nerve (right &left)/ optic chiasma	52 years when target is oropharynx

IMRT Planning

- Coplanar multiple fields around the isocentre using isotropic gantry angles were used and may be adjusted slightly to avoid the beam entry through OAR's.
- In next step of fluence optimization, the dose coverage minimum and maximum required for PTV and dose tolerance to OAR's was defined.
- Optimize fluence was calculated for LINAC specification.
- Now the plan was evaluated by two methods- isodose coverage and DVH.
- Plan may be compared with an alternate plan, to improve treatment quality.

Dosimetric Assessment

Dose–volume histograms (DVHs) corresponding to the delivered IMRT plan were generated for each arm.

Dosimetric parameters assessed in PTV (95 to 107%):

- D95 (Gy): Dose received by 95% PTV
- Dmax D_2: Maximum dose received by PTV
- Dmin D_{98}: Minimum dose received by PTV
- Dmean D_{50}: Mean dose received by PTV
- Homogeneity Index (HI)

$$\text{Homogeneity index (HI)} = \frac{D2(Gy) - D98(Gy)}{D50(Gy)}$$

- Conformity Index (CI)-

$$\text{Conformity Index (CI)} = \frac{\text{Treated volume (TV)}}{\text{Planning Target Volume (PTV)}}$$

Where TV is treated volume i.e., volume receiving 95% of the prescribed dose, PTV is planning target volume.

Dosimetric assessment of OAR's

Dose constraints of OARs according to RTOG and QUANTEC as per department protocol.

Dosimetric parameters assessed in RVR

- RVR- *Dmean, v5(%), v(10%), v(20%),v(30%), v(40%), v(50%), v(60%), Dmax was seen.*

Radiation Toxicities

- Radiation Therapy Oncology Group (RTOG) assessed skin, mucosal and salivary gland toxicities by acute and late morbidity scoring criteria.
- Acute RTOG morbidity criteria apply from day of radiotherapy commencement till 90 days. Patients were assessed weekly during chemoradiation for assessment of acute radiation reactions.
- Late radiation reactions were assessed using RTOG late morbidity criteria that will be applicable from 90 days onwards.
- During treatment, assessment was done on a weekly basis and thereafter monthly basis by Common Terminology Criteria for Adverse Effects, CTCAE (v4.03)

Clinical Response Assessment

The patients were assessed for objective tumor response according to WHO criteria:

- Complete response (CR): Total tumor regression for at least 4 weeks
- Partial response (PR): 50% or more reduction in the product of two major perpendiculars of the measurable tumor for at least 4 weeks.
- Stable disease (SD): Less than 50% or more reduction to less than 25% increase in cross product
- Progressive disease (PD): Growth of measurable tumor by 25% or more or appearance of new lesion.

Follow up

- Patients were assessed weekly during radiotherapy, at the end of radiotherapy and thereafter monthly up to 6 months.

Statistical Analysis

- Data analysis was performed using the Statistical Package for Social Sciences (SPSS)
- An unpaired t-test was used to compare mean of two independent groups.
- Chi-square test was used for statistical analysis of

compliance and toxicities. p <0.05 was considered statistically significant.

RESULTS

The median age in both groups was 55 years with male to female ratio 24:1. The most common addiction was smoking (70%) followed by tobacco chewing (60%). The common symptoms were weight loss (82%) and difficulty in chewing (74%). The oropharynx is both groups' most frequently involved subsite (48%). A total of 86% belonged to locally advanced stage (AJCC III & IV).

There were no grade IV skin reactions in either group, though grade 3 reactions were more in group 1. None of the patients had grade 4 xerostomia. Grade 3 xerostomia was common in group 1 in comparison to grade 2 xerostomia in group 2.

During radiotherapy, no grade IV mucositis was seen in group 2, whereas group had in 12% of patients; further grade III mucositis was commonest in group 1 (44%) in comparison to lesser grade II mucositis in group 2 (64%). (Table 1)

After radiotherapy, in follow-up of one month, grade III mucositis was persistent in all patients of group 1 (44%) in comparison to group 2 where none had grade III mucositis and only 16% had grade II mucositis (Table 2).

Dosimetric parameters of PTV and dose constraints for OARs were achieved in all patients in both groups and no statistical difference was found (Tables 3 and 4).

D_{mean} dose of 30Gy for RVR was achieved in 92% (n=23) patients in both groups 1 and 2 group 1. Dosimetric parameters for RVR in group 1 and group 2 did not reveal any statistical difference (Table 5).

Table 1: Mucous membrane reactions during radiotherapy

Mucositis grade	*N (%)*	
	Group 1	*Group 2*
0	0	1(4%)
I	1(4%)	6(24%)
II	10(40%)	16(64%)
III	11(44%)	2(8%)
IV	3(12%)	0(0%)

Table 2: Mucous membrane reactions after radiotherapy

Mucositis grade	*N (%)*	
	Group 1	*Group 2*
0	0	6(24%)
I	1(4%)	15(60%)
II	13(52%)	4(16%)
III	11(44%)	0(0%)
IV	0(0%)	0(0%)

Table 3: Dosimetric parameters of PTV in both groups

PTV parameters	*Group-1*	*Group-2 (RVR)*	*p-value*
V95(%)	93.25	94.70	0.38
D2	71.80	71.70	0.33
D50	70.42	68.80	0.08
D98	68.09	67.40	0.35
D100	46.25	52.86	0.08
Dmin	46.25	52.19	0.07
Dmax	73.73	73.29	0.11
Homogenity index	70.32	0.06	0.21
Conformity index	1.12	1.12	0.46
Dmean	70.32	70.00	0.16

DISCUSSION

Radiation in head and neck cancers have common complications – acute like skin reactions and mucositis and chronic like dryness of mouth. The acute reactions of skin may vary from discoloration to wet desquamation of skin while mucosal reactions may present as slight mucositis to severe reactions like bleeding ulcers. Mucositis is the main concern during radiotherapy which may lead to discomfort to the patient in terms of pain and difficulty in swallowing food. It results in poor nutritional intake and poor healing process of damaged normal tissue. This inadvertent cycle ultimately may lead to interruptions in radiotherapy and treatment failure.

In a study by Denham *et al*., where 70 gy over 47 days were delivered in treating head and neck cancers, grade-3 oral mucositis was the most common reaction found in the patients during treatment.[2] Similarly, Otter *et al.* in his study evaluated complications in head and neck cancer patients receiving radical treatment.[3] The patients received chemotherapy and radiotherapy for oral and pharyngeal cancer and had grade 3 oral mucositis during treatment. Similarly, in the present study grade-3 oral mucositis was seen in patients of group 1 where RVR was not delineated and grade of oral mucositis was reduced in group 2 patients, where RVR was delineated. The main reason was that since the region of clinical interest was identified as OAR, the planning restricted the dose to RVR and less dose dumping was done in this region.

In a study by Sanguineti *et al.* where they showed correlation between 3F technique and IMRT technique, showed that mucosal sparing for oropharyngeal cancer was possible at dose constraints of 30 Gy, which was similar to our study where we applied dose constraints of Dmean 30 gy and found reduction in grade of oral mucositis in group-2(RVR), as compared to group-1 where no dose constraints was described hence, Dmean of 30 Gy seems adequate in reducing oral mucositis.[4]

In a study by Reddy *et al*., evaluated the risk of dose dumping in normal tissue by IMRT plans in head and neck cancer, cervix and prostate cancer, and concluded

Table 4: Dosimetric parameters of OARs in both groups

OAR's	*Dosimetric parameters*	*GROUP-1*	*GROUP-2 (RVR)*	*p-value*
Right Parotid	D_{mean}	37.97	34.05	0.05
Left Parotid	D_{mean}	35.80	33.09	0.19
Both Parotids	D_{mean}	37.39	33.89	0.69
PRV Spine	D_{max}	47.02	45.48	0.04
Brain stem	D_{max}	37.53	32.94	0.12
Optic chiasma	D_{max}	2.88	2.57	0.21
Right Optic Nerve	D_{max}	2.66	2.56	0.38
Left Optic Nerve	D_{max}	2.67	2.43	0.19
Right Cochlea	D_{mean}	16.71	14.42	0.23
Left Cochlea	D_{mean}	14.69	13.26	0.31
Right Eye	D_{max}	2.81	2.79	0.48
Left Eye	D_{max}	3.62	2.85	0.42
Right Lens	D_{max}	1.85	1.71	0.18
Left Lens	D_{max}	1.81	1.69	0.22
Lips	D_{mean}	21.10	20.66	0.44
Mandible	D_{max}	70.55	70.40	0.46

that, adjusting the beam angles for normal structures and constructing phantom structures can decrease dose dumping to 85%.[5] Similarly in our study Dmean of RVR in group-1 was 23.68 and Dmean of RVR in group-2(RVR) was 22.96, and the difference is of only 0.72 in the present study, contouring the RVR and giving it a dose constraint resulted in a negligible decrease of only 3%, though clinically we could appreciate a decrease in the mucositis grade.

In a study by Pauloski *et al.*, evaluated the relationship between oral mucositis changes and its effect on oral intake, concluded that patients who had more mucosal alteration during radiotherapy had decreased oral intake.[6] In our study we found that in group-1 where no dose constraints were applied to RVR, had higher rates of mucosal reactions and poor oral intake during radiotherapy, whereas in group-2 (RVR), where dose constraints were applied to RVR, patient had less severity of mucosal reactions and had better oral intake, this is due to optimization of RVR in patients of group-2 (RVR), which lead to decreased dose dumping in oral mucosal areas and hence the severity of oral mucosal reactions were reduced.

Table 5: Dosimetric parameters of RVR in both groups

Dosimetric parameters of RVR	*Group-1*	*Group-2 (RVR)*	*p-value*
Dmean	23.68	22.96	0.32
V5(%)	84.71	82	0.29
V10(%)	69.56	67.70	0.34
V20(%)	50.18	48.1	0.29
V30(%)	32.57	31.3	0.34
V40(%)	19.77	19.50	0.48
V50(%)	11.44	11.8	0.39
V60(%)	5.41	5.63	0.41
Dmax	71.21	72.37	0.16

Sanctis *et al.* showed the importance of patients receiving radiation therapy (RT) with or without systemic therapies is oral and oropharyngeal mucositis.[7] They present with symptoms like pain, bleeding, dysphagia, infections, and difficulty eating, unintentional weight loss before therapy, immunosuppression due to comorbidities (such as diabetes mellitus) or aged patients, that were already present at the time of diagnosis, their eradication might reduce the severity of mucositis during treatment. In our study 82% of the patients had weight loss history, Weight loss in head and neck cancer patients during RT is related to the acute toxicities of radiation and concomitant chemotherapy. Critical weight loss (the involuntary weight loss of ≥5% during the radiation course) as a known negative prognostic factor increases the mortality rate in head and neck cancer patients. The decline of immune function, increasing the risk of infection, and the need for antibiotics are directly related to critical weight loss, and high grade of mucositis also seen in such patients. To prevent the weight loss, the patient was advised to increase oral intake by changing the consistency and flavor of the food, he was also advised to increase water intake during the entire course of the treatment to possibly help to decrease mucositis. The patient was also given parenteral nutrition and supportive care to prevent weight loss.

In a study by Vijayakumar *et al.* patients with head and neck cancer who had RT were enrolled in the study.[8] In the first one to four weeks of treatment, oral mucositis peaked (60%). They concluded that mucositis is a painful side effect caused by the inflammatory reaction of epithelial mucosa to the cytotoxic effects of chemotherapy and radiotherapy**.** In another study, Nagarajan *et al.* evaluated the patients receiving chemoradiotherapy and were monitored throughout their course of treatment and concluded that by monitoring the vitality and maturation of oral mucosal cells during radiotherapy by IMRT technique, oral mucositis can be quantified at the cellular level and can decrease the incidence. In our study, the degree of oral mucositis was clinically evaluated

during weekly follow-up and it was found that group-1 had more mucositis patients compared to group 2 (RVR). During clinical evaluation of oral mucositis if severity increases, the patient was conservatively managed, and it was observed that (grade -3) oral mucositis was seen in 44% of individuals in group-1, and grade -2 oral mucositis in (64%)in group-2(RVR) because mucositis caused by radiation usually starts at doses of 15 to 20 Gy of conventional fractionated radiation therapy since it is a function of cumulative tissue dose. Typically, doses of 30 Gy are when ulcerative mucositis is observed, which normally occurs during the course of radiotherapy because of the dose dumping into the normal tissue. this leads to clinical symptoms of pain which further hampers the nutrition of the patients. If we can control mucositis, we may be able to control pain and mucositis. In group-1 grade-III oral mucositis was prominent because apart from the target volume, the remaining volume at risk was not contoured and dose prescription was also not given to the normal tissue. Whereas in group-2, grade -II mucositis was most prominent, suggesting there were fewer reactions in the group where the normal tissue classified as remaining volume at risk was contoured and mean 30 GY dose was prescribed. Hence, RVR is clinically important.

In a study by Abdennebi A *et al.* comparison between IMRT and DAT (dynamic arc therapy) was done and concluded that dynamic arc therapy reduces the dose not only to OAR but also to RVR, keeping the same PTV coverage. In our present study, all patients were planned by IMRT and all patients irrespective of RVR was delineated or not had achieved PTV dosimetric parameters.[9]

Ali *et al.* studied the comparison between VMAT and IMRT in remaining volume at risk was done, In RVR volumes that got 15, 10, and 5, which are (4327, 5281, and 6703cc) and a 1019c Gy mean dose in the VMAT approach, compared to (4435, 5311, and 6543 cc) and a 1051c Gy mean dose in IMRT, VMAT has an advantage over IMRT.[10] They concluded that IMRT has the least volume for V5Gy, VMAT has an advantage for V15Gy, V10Gy, and the mean dosage of RVR. they concluded that IMRT has the least volume for V5Gy, VMAT has an advantage for V15Gy, V10Gy, and the mean dosage of RVR. In our study we treated all the patients by IMRT technique and the parameters used to evaluate RVR Dmean, v5(%), v(10%), v(20%),v(30%), v(40%), v(50%), v(60%), Dmax the mean of respective volume were 22.96, 82, 68, 48, 31, 20, 12, 5.6, 72.36. We would like to conduct further study in our institute to see the outcomes in tumor control and side effects using VMAT technique.

Khattar *et al*., in her study included 20 head and neck cancer patients and concluded that oral mucosa should be identified as a pseudo OAR and further clinical research must optimize the dose limitations in order to potentially reduce the prevalence and severity of oral mucositis.[11] In our study D_{mean} 23.68 and D_{max} 71.20 in group 1 and D_{mean} 22.96 D_{max} 72.36 in group 2. There is a slight lower difference in the D_{max} and D_{mean} in patients where RVR was contoured which led to a slight decrease in the severity of oral mucositis. It suggests that oral mucosa or RVR should be contoured on daily basis so that dose dumping can be decreased in these regions.

CONCLUSION

IMRT plans help to decrease the doses to RVR. The delineation of RVR and prescribing dose constraint decreased the severity of oral mucositis clinically, but significant difference could not be seen in the dosimetric parameters of RVR. We recommend delineating and prescribing dose constraints to RVR to decrease acute oral mucositis in head and neck cancer patients undergoing chemoradiotherapy.

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