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Impact of Repeat-CT on Doses to Target Coverage, Parotid Volume and Organs at Risk During Course of Radiotherapy in Head and Neck Cancer

Sumit Gupta[1], Jayeeta Sen[2], Amresh Kumar[3], Ridhima Ojha[4], Saurabh Karnawat[5], Virender Bhandari[6]

Author's Affiliation: [1]Senior Resident, [2,3,4]Registrar, [5]Assistant Professor, [6]Professor, Department of Radiation Oncology, Sri Aurobindo Medical College and PG Institute, Indore, Madhya Pradesh 453555, India.

Corresponding Author: Virendra Bhandari, Professor and Head, Department of Radiation Oncology, Sri Aurobindo Medical College and PG Institute, Indore, Madhya Pradesh 453555, India.

E-mail: virencancer@yahoo.co.in

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Abstract

Head and neck cancer is one of the most common malignancies in India. IMRT technique results in better sparing of OAR and homogenous dose distribution to the target. Adaptive radiotherapy is another step forward in that direction. We did a repeat CT scan during the radiotherapy treatment course followed by recontouring and replanning which resulted in better coverage to PTV and resulted decreased dose to OARs. In our study we found that mean difference between CTV and PTV volumes between Actual Plan and Hybrid Plan is 69.95 (p value 0.001) and 109.24(0.001) respectively. There was a significant reduction in doses received by both parotids. Right parotidgland received 3.03 Gy less in actual plan as compared to hybrid plan and Left parotid gland showed difference of 1.97 Gy between both the plans. Also, the D mean in right Eye was in AP 15.38 ± 10.56 and that of HP19.34 ± 11.27 with a mean difference of 3.96 (p value = 0.001); left eye, the D mean dose with AP 14.43 ± 9.15 and that in HP 18.33 ± 10.24 with a mean difference 3.89 (p value=0.001).

Keywords: Head and neck cancer; Adaptive radiotherapy; IMRT.

Introduction

Head and Neck malignancies are one of the common cancers worldwide, As per Globocon 2020 Head and Neck cancers contribute to 10.3 % of all cancers and 8.8% of all cancer deaths in India.[1,2] Histologically, squamous cell carcinoma makes up 90% of the head and neck cancer, most commonly involving tongue followed by buccal mucosa, gums, tonsils.[3]

Radiation treatment aims at delivering a precisely measured dose to the target tumour site to ensure maximum tumoricidal effect and minimum toxicities resulting in better quality of life and prolonged survival of the patients.[4]

Since 1980 Radiation therapy technique has seen immense advancement from 2Dtechnique to Intensity-modulated radiotherapy (IMRT). IMRT is the technique of choice for head and neck cancers due to precise dose distribution and better sparing of Organs at Risk (OAR). In order to further improve dose homogeneity to target and to reduce doses to OAR, IMRT has evolved into adaptive RT which provides steep IMRT dose gradient. With conventional IMRT the actual delivered dose may not correspond to the planned dose because of setup error and anatomical modifications, resulting in an increase in the doses delivered to organs at risk (OAR) and/or a decrease in the doses delivered to the tumour, causing increased risk of

toxicity and recurrences. We aimed to assess the discrepancies in planned and delivered dose and their effects on OAR 'sin H&N cancer patients, by re-imaging and re-planning after 18 to 20 fractions and the remaining plan was delivered by Adaptive Radiotherapy Technique (ART).Adaptive radiotherapy may be divided into two categories: anatomy-adapted (A-ART) and response-adapted ART (R-ART). In A-ART re-planning of patients is based on the concept of structural and spatial changes occurring over treatment, with the intent of reducing over dosage of sensitive structures such as the parotids, improving dose homogeneity, and preserving coverage of the target. In contrast, response-adapted ART is the process of re-planning patients based on response to treatment, such that the target and/or dose changes as a function of interim imaging during treatment, with the intent of dose escalating persistent disease and/or de-escalating surrounding normal tissue.

The Aim of this study was to show the benefit of repeat computerized tomography and re-planning in selected head and neck patients during the course of radiotherapy.

Materials and Methods

This was a prospective observational study in which 60 patients with various head and neck cancer (oropharynx, hypopharynx, larynx, tongue, nasopharynx was selected) were included between January 2015 to May 2019. The inclusion criteria were confirmed histological cases of head and neck cancer between 18-65 yrs of age who gave consent, with no metastatic disease and with Karn of sky score (KPS) of >80%. Clinical staging was defined according to the 2017AJCC classification 8th edition.[5] Our study cohort consisted of patients who presented with locally advanced disease. They were treated with concurrent radiotherapy along with weekly cisplatin-based chemotherapy.

For CT simulation, an immobilization mould was made to stabilize the patient.[6,7] Image acquisition was done by computed tomography (CT) using 3mm slice thickness.

After transfer of the images to treatment planning system, delineation of the tumor targets and surrounding organ at risk was done. IMRT planning was done five to seven beams placed around the patient at different gantry angles. During the treatment, intensity and the shape of the beam is modulated with the help of Multi-leaf collimators (MLCs) and collimator.[8,9] AAAalgorithm was applied for dose calculations. A laser installed in the Linacroom was used to ensure the patient positioning. Moreover, positioning was validated with KV or CBCT images.[10]

All patients receiving RT were taken up for repeat CT scan during the fourth week of RT i.e after 15th -20th fraction for which another immobilisation mould was made followed by a repeat CT scan was done as maximum weight loss and changes in tumor size (tumour regression clinically) were observed during this time and re-planning with IMRT plan was done.[11,12] During recontouring of the targets and the OAR's attempts were made to maintain the original margins such that exact volume changes can be noted.

According to anatomical changes on repeat CT scan, CTV 54 volumes were changed. Then we generated two plans on repeat CT scan for the remaining fractions. One Actual plan (AP) generated by planning on repeat CT scan and a second Hybrid plan (HP) was generated (without repeat CT scan) which is the plan on the original CT Scan which is superimposed on this repeat CT Scan. This gave a clear idea of the changes in the volumes of the target and changes in the doses to the OAR's clearly. This matching was confirmed by the physicist and physician. Actual Plans that are generated on repeat scan were used for delivering the remaining fractions.

The change in volume and doses of each was calculated and statistical significance was calculated using paired t test with a P value <0.05 as significant.

In the IMRT plan, the dose prescriptions were given for CTV, PTV and OARs mainly Parotids, Spinal cord and eye lens. Dose constraints used for tumor target volume was as per RTOG guideline and dose constraints for OARs was as per QUANTEC guidelines. Then IMRT plans were generated and approved on treatment planning system Eclipse version 13.7 (Varian Medical Systems, Palo Alto, CA).

Volumetric and dosimetric parameters were compared on the dose-volume histogram (DVH) on repeat CT scan between actual plan and hybrid plan. Homogeneity and conformity index of both plans were assessed for accuracy of each plan. For remaining fractions comparisons of dosimetry of PTV54 and CTV54 was done between AP and HP (Figure 1).

The objective of this study is to compare the target doses received by the actual plan (AP) that is the plan with repeat CT scanand hybrid plan (HP) that is the plan without repeat CT scan, and also compare volumetric and dosimetric parameters for

target structure (like CTV and PTV) and OARs (like right and left Parotid) with the help of DVH. The homogeneity index (HI) and conformity index (CI) and the PTV coverage help to assess the accuracy of both plans (actual plan and hybrid plans) on repeat scan.

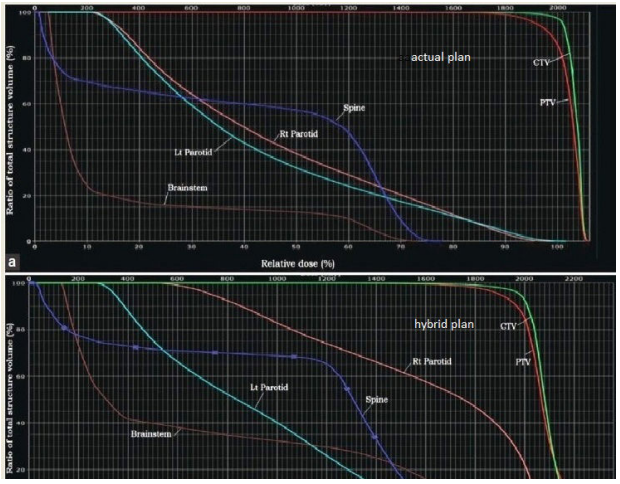

Fig. 1: DVH for different OAR's and PTV.

HI = D5/D95 Where D5 – dose to 5% volume of PTV, D 95 – dose to 95% volume of PTV. HI typically range from 0-1

CI = (TV 95/PTV) Where TV 95 volume of target covered by 95% isodose line, PTV- the volume of the PTVCI typically range from 0-1.

For comparisons between the CT volumes and doses to OARs Paired 't' test applied. P value <0.05 was taken as statistically significant. All statistical analyses were conducted using SPSS (originally Statistical Package for the Social Sciences) statistical software version 15.

Result

In this study it was seen that the Volume changes were significant for CTV 54 and PTV 54 as there was tumour shrinkage (Figure 2). Mean difference between CTV and PTV volume between Actual plan and Hybrid plan is 69.95 cc(p value 0.001) and 109.24 cc (p value 0.001) respectively (Table1).

Table 1: Comparison of Volume changes between AP and HP.

Parameter	AP Mean ± SD	HP Mean ± SD	Mean Difference	t Value	p Value
CTV 54 volume (cc)	148.32 ± 47.41	218.27 ± 66.11	69.95	15.523, df=59	0.001*
PTV 54 volume (cc)	255.56 ± 120.23	364.80 ± 177.69	109.24	9.602, df=59	0.001*
PTV D95 (cc)	98.47 ± 1.76	94.48 ± 2.21	3.99	15.527, df =59	0.001*
PTV D99 (cc)	92.31 ± 2.51	87.51 ± 4.07	4.80	10.123, df=59	0.001*
Right parotid volume (cc)	17.85 ± 4.17	19.37 ± 4.51	1.52	5.441, df=59	0.001*
Left parotid volume(cc)	17.00 ± 4.64	18.07 ± 4.26	1.07	4.345, df=59	0.001*

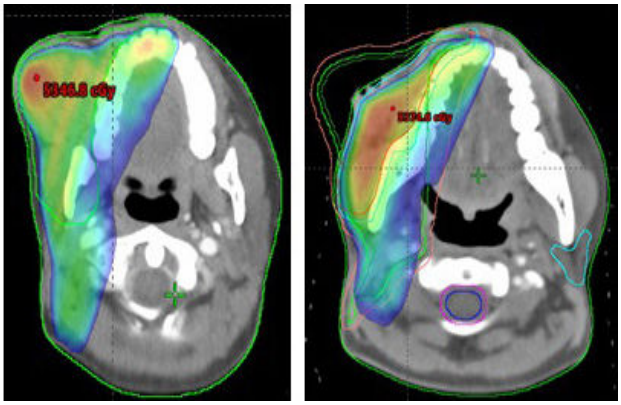

Fig. 2: First and Repeat CT dose volume comparison.

The comparison of mean CTV and PTV volume in actual plans (AP) and hybrid plans (HP).The mean CTV volume in the HP was 218.27 ± 66.11cc, while in the AP it was 148.32 ± 47.41 cc, with a mean difference of 69.95 cc. There was a significant reduction in the CTV volume in the AP in comparison to the HP (p=0.001). The mean PTV volume in theHP was 364.80 ± 177.69 cc, while in the AP it was 255.56 ± 120.23 cc, with a mean difference of 109.24 cc. There was a significant reduction in the PTV volume in the AP in comparison to theHP(p=0.001). So, there was a significant reduction CTV and PTV volumes in the AP in comparison to the HP. (Table 2)

Table 2: Comparison of doses received by OAR between AP & HP.

Parameter (Gy)	AP MEAN ± SD	HP MEAN ± SD	Mean Diff.	t Value	p Value
Rt Parotid Dmean	13.79 ± 7.78	16.82 ± 8.38	-3.03	11.321, df=59	0.001*
Lt Parotid Dmean	14.96 ± 5.02	16.94 ± 5.24	-1.97	14.987, df=59	0.001*
Right Eye Dmean	15.38 ± 10.56	19.34 ± 11.27	-3.96	16.691, df=59	0.001*
Left Eye Dmean	14.43 ± 9.15	18.33 ± 10.24	-3.89	16.761, df=59	0.001*
Right lens Dmax	3.25 ± 2.04	5.34 ± 2.57	-2.09	13.466, df=59	0.001*
Left lens Dmax	2.80 ± 1.74	5.00 ± 2.22	-2.20	13.575, df=59	0.001*
Spine Dmax	20.93 ± 8.19	24.24 ± 8.30	-3.31	15.609, df=59	0.001*

The mean right parotid volume in the HPwas 19.37 ± 4.51 cc, while in the AP it was 17.85 ± 4.17cc, with a mean difference of 1.52 cc.this wasstatistically significant (p=0.001). The mean left parotid

volume in the HP was 18.07 ± 4.26 cc, while in the AP it was 17.00 ± 4.64 cc, with a mean difference of 1.07 cc. Though there was a slight reduction in the left parotid volume. this reduction was significant (p=0.001), There was a significant reduction in the right parotid and left parotid volume (p=0.001), showing a larger right pharotid and left volume in the hybrid plan in comparison to the actual plan. ((table1

Dosihmetric comparison was done for PTV54 for all the patients. The mean D95 in the AP was 98.47 ± 1.76, while in HP it was 94.48 ± 2.21. There was a significant decrease in the D95 in the HP in comparison to the AP (p=0.001).

The mean D99 in the AP was 92.31 ± 2.51, while in HP it was 87.51 ± 4.07. There was a significant decrease in the D99 in the HP in comparison to the AP (p=0.001). The mean D95 and D99 have significantly reduced in the HP in comparison to the AP.

The doses to the parotid gland were also reduced due to replanning. The right parotid showed dose of 13.79Gy on AP and a dose of 16.82 on HP with a mean difference of 3.03 Gy and the left Parotid received 14.96 on AP whereas 16.94 on HP with a mean dose reduction of 1.97Gy. These had a p value of 0.001 and 0.001 respectively which are statistically significant.

The mean of the maximum dose (Dmax) to spine in the AP was 20.93 ± 8.19, while in the HP it was 24.24 ± 8.30. There was a significant increase in Dmaxto spine in HPin comparison to AP (p=0.001). Dmax of spine was higher inHP as compare to AP. (table 2)

The Dmeanof right eye in the AP was 15.38 ± 10.56, while in the HP it was 19.34 ± 11.27. There was a significant increase in the Dmeanof right eye in the HP in comparison to the AP (p=0.001).

The Dmeanof left eye in the AP was 14.43 ± 9.15, while in the HP it was 18.33 ± 10.24. There was a significant increase in the Dmeanof right eye in the HP in comparison to the AP (p=0.001). Dmeanin both Eye was higher in the HP in comparison to the AP.

The mean of Dmax to the right eye lens in the AP was 3.25 ± 2.04, while in HPit was 5.34 ± 2.57. There was a significant increase in the mean of Dmax to the right eye lens in the HP in comparison to the AP (p=0.001). (table 2)

The mean of Dmax dose to the left eye lens in the AP was 2.80 ± 1.74, while in the HPit was 5.00 ± 2.22. There was a significant increase in the mean of Dmax dose to the left eye lens in the HP in comparison to the AP (p=0.001).The mean of Dmaxof both Lens was higher in the HP in comparison to the AP.(Table 2).(Table 2)

Discussion

Multi-modality treatment is preferred in Head-and-neck cancer treatment depending upon the stage and post-op histological features. The aim of our study was to detect the influence of repeat CT scan and re-planning during the course of radiotherapy with IMRT technique. We generated two plans HP and AP during the second half of treatment and assessed both the plans. We found that there was a significant decrease in the coverage of target volume (especially with PTV) with HP and also showed increased dose to the normal structure, while AP showed improved target coverage along with the decrease in doses to normal organs which resulted in decrease in treatment related toxicities.[13] Our study results were statistically significant.

Doses to normal organs significantly increase due to volume reduction of the target if Re-CT and/or re-planning is not done in H & N cancer.[10-13]

Concurrent administration of chemotherapy along with radiotherapy leads to significant weight loss in patients with high BMI (body mass index) and thereby increases the chances of reduction in CTV due to tumour volume changes. Hence, ReCT scan and re-plan is mandatory in patients with BMI > 25.[14,15]

As per Beltran et al.[16], in patients treated with IMRT, weight loss can be considered as an important parameter to analyse changes in irradiated areas. We delineated tumour volume and OARs as per recent guidelines.The mean reduction that we noticed was of 7.5% in the mean volume of CTV due to changes like weight loss, tumours or nodal shrinkage, and the changes in anatomic space at risk.

Castelli et al.[17], conducted a study where the re-planning was done during the 3rd or 4th week of treatment. Reduction in doses was found in Parotid gland Dmean,spinal cord Dmax of up to 4.1 Gy&4Gy with ART, and also coverage ofPTV (D95%) increased by 2.1, median follows up of 29 to 38 months. Similarly, in our study, there was a significant change in the doses to left and right parotid between the actual and hybrid plans. We also found that thechange in of mean PTV (D95) which resulted in reduction in toxicity due to less dose to OARs. Bhandari et al.[18] conducted a similar study with 15 patients with primary H&N

cancer. The mean difference in volumes between CT and repeat CT were 44.32 cc, 82.2 cc, and 149.83 cc for GTV, CTV, and PTV, respectively. For AP the mean CI and HI was 0.68 and 1.07, while for HP it is 0.5 and 1.16 respectively. Mean D95 and D99 of PTV was 97.92% (±2.32) and 93.4% (±3.75), respectively for AP and 92.8% (±3.83) and 82.8% (±8.0), respectively for HP. Increase in the doses to OARs such as right parotid, left parotid, spine, and brainstem were 5.56 Gy (Dmean), 3.28 Gy (Dmean), 1.25 Gy (Dmax), and 3.88 Gy (Dmax), respectively in HP as compared to AP. Similar results were seen in our study.Burelaet al.[19] showed in his study of 10 patients of head neck cancer that if the re-planning is done in 4th week during the treatment. The reduction in doses to ipsilateral parotid (mean % decrease is 27.3%p=0.008) and contralateral parotid (24.63%, p= 0.008) is significant. There is reduction in PTV (146.3 cc, 13.1%, p= 0.034). Similar result was seen in our study, in which we found reduction in PTV, CTV, parotid volume and significant dose reduction in PTV, CTV and OARs. Barker et al.[14] showed significant tumour volume reduction along with a shift in the centre of the tumour mass. There was a significant change in the volume of Parotid gland volume with the change in the tumour volume.

Wang et al.[11] conducted a retrospective a study on 28 patients of nasopharyngeal carcinoma. With re-planning their results showed a reduction in point dose to the spinal cord, left parotid mean dose and right parotid V30 by 5Gy, 4.2Gy, and 3.2% respectively. In our study, Dmean to right parotid and left parotid decreased by 1.52 Gy and 1.07Gy respectively. Tamaki Nishi et al.[20] did a study, with twenty patients with pharyngeal carcinomas and treated them on two-step IMRT at the third or fourth week of treatment a second planning CT was done, parotid gland shifted medially on an average of 4.2 mm on CT-2. The mean doses to parotid glands on the initial plan (CT-1) were 25.2 Gy and on the second (transferred) plan was 30.5 Gy. The D2 (dose to 2% of the volume) doses of initial and transferred plan for spinal cord were 37.1 Gy and 39.1 Gy, respectively. This led them to conclude that the two-step IMRT method could adapt to changes in body contour, target volumes and risk organs as an adaptive RT scheme during IMRT treatment. Capelleet al.[21] conducted a prospective study on 20 patients with mid-treatment re-planning. They found that there showed no use of routine adaptive re-planning in all the patients, as there were no benefits in patients who did not undergo any tumour shrinkage or weight loss during the course of RT. In a comparative study, we included only those patients who underwent these anatomical changes in tumour volume.

The short-comingswe saw with this study was that deformable registration of the two planning CT scan was not used. Hence, the accuracy of CT registration was not found to be predictive of benefit level for any target or OARs, and therefore any errors that may have related to the accuracy of registration of CT was not considered significant to affected our results. It was not possible to accurately summate the dose statistics from both the parts of treatment plans without the deformation process of matching each study, each dose voxel between the two CT scans (the initial and the re-planning). Although the adopted and non-adopted portion of the treatment could directly be compared.

Knowing some of the limitationsand also the recent improvements that have been successfully made with the deformation software it still needs to be used with caution until a centre has experience with it in their context especially concerning computer-generated automatic segmentation.

With our study, the relevant tumour volume and normal tissue volumes for the first and the second plan was drawn by the same radiation oncologist on each CT scan for initial planning and then for the re-planning CT scan, which is considered gold standard in target and normal tissue volume delineation. Some of the limitations in implementing the repeat CT scan imaging and re-planning that we faced were the increased workload for the physicist and dosimetrist, increase in the timing of the radiation oncologist in recontouring of target volumes and normal structure, increased the workload of clinical staff, increased use of limited simulation and treatment time on the machine.

On patients part one of the major limiting factor in implementation of Re-CT and re-planning methods was financial constraints. So, the results of this study should not be applicable for all the H & N cancer patients, who are undergoing radiation treatment. This study was conducted on a highly selective patient group. Those who were identified retrospectively and prospectively as of the patient group with locally advanced, non-metastatic tumour and had clinically appreciated tumour shrinkage and /or weight loss duringthe course ofradiotherapy with IMRT technique.

In conclusion, during the six week course of radiotherapy treatment there is weight loss, tumor shrinkage OAR shrinkage and also changes in the patient position and anatomy which leads

to changes in dosimetric parameters of the target volume as well as the surrounding normal tissues hence Re-CT and re-planning twice during the course definitely reduce the chances of differences in delivered dose due to volume changes and improved coverage of target volume and reduction in doses to OARs hence reducing the acute and late toxicities that leads to improved survival and better quality of life ultimately leading to better prognosis.

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