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DOSIMETRIC ANALYSIS OF ADAPTIVE RADIOTHERAPY(ART) IN LOCALLY ADVANCED HEAD AND NECK CANCER

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ABSTRACT **PURPOSE/OBJECTIVE:** The objective of this study is to evaluate the dosimetric parameters in adaptive radiotherapy for locally advanced head and neck cancers

METHODS AND MATERIALS: This is a Hospital-based Prospective study conducted in the period from Dec 2020 to March 2021. Histologically proven Head and Neck Carcinoma patients with Stage III to IV (locally advanced) were selected for the study. A total of 10 patients receiving definitive, conformal radiation therapy to the head and neck region were evaluated for the study. After the acquisition of CT images, target volumes, OARs were contoured in the planning CT. Images were again acquired midway during the planned course of radiation therapy. Body contours, target volumes, and organs at risk were redrawn on the new set of images. Two sets of additional treatment plans were generated: 1) a non-optimized plan (plan 2), which is an overlay of the original plan (plan 1) on the new set of contours, and 2) an optimized plan(plan 3) with the new set of contours. These 3 sets of plans were then compared for dosimetric differences.

RESULTS: Four patients had locally advanced nasopharyngeal cancers, 4 patients had locally advanced oropharyngeal cancers, 2 patients had locally advanced hypopharyngeal cancer. The average reduction in gross tumour volume was 37.1 ml. The average changes in right and left parotid volume were 5.94 and 5.49 ml, respectively. With the non-optimized plan, the average increase in the maximum dose to the spinal cord was 9.8% (58.96-68.76; p= 0.156). With reoptimization, the maximum dose to the spinal cord decreased from 68.76% to 54.97% (mean difference, -13.79%, p=0.03). The average D99 for the planning target volume(dose received by 99% of the target volume) was 98.68% and 98.65% with the original and reoptimized plans, respectively. Most of the patients during radiation had Grade 2 skin toxicity and Grade 2 mucositis which was managed conservatively.

CONCLUSIONS: This study demonstrates that during radiation there is gross changes of volumes in locally advanced head and neck cancers and thus adaptive radiation therapy plays a pivotal role in locally advanced head and neck cancer.

KEYWORDS : IMRT/IGRT, locally advanced head and neck Cancer, Adaptive Radiotherapy, Dosimetry

INTRODUCTION

Head and neck cancers (HNC) constitute around 30% of all types of cancers in India. Around 60-80% of HNC patients in India present with advanced disease stages as that of the developed countries where the count is only 40%. According to GLOBOCAN 2018 in India, the number of new lip and oral cavity cases in both sexes in all ages is 10.4%. (1). As per the three years data of PBCR 2009-2011 proposed by the National Cancer Registry Programme (NCRP), in Kamrup District of North East India, states that the Relative Proportion (RP) of total HNC among the males and female are 26% and 12% respectively.

Among the males, the most prevalent type is cancer of the hypopharynx (RP: 8.3% and AAR 14.7) followed by the tongue (RP: 5.4% and AAR 9.4) and mouth (RP: 4.3% and AAR 7.7). In females, the most prevalent is mouth cancer (RP: 4.25% and AAR 7.6) followed by tongue cancer (RP: 1.99% and AAR 3.2). (2) The prognosis rate of HNC is very poor with 50%-60% recurrence and 20%-30% of metastases within the two years of treatment. (3)Tobacco intake is one of the contributing factors for head and neck cancers (HNC). According to the Global Adult Tobacco Survey 2, 2016-2017, in India, the prevalence of current tobacco smoking in Assam is 13.3%. Mizoram is the highest at around 34.4%. The prevalence of use of current smokeless tobacco in Assam is 41.7%. (4)

To date, there is a lack of proper evidence that individuals with low socioeconomic status are more susceptible to the development of HNC albeit with no history of smoking and alcohol intake. (5)

The majority of the HNC present with advanced stage III or IV, requiring a multimodality treatment and radiotherapy (RT) and concurrent chemotherapy are the major non-surgical mode of treatment. RT is mainly done to control the locoregional spread in both early and advanced stages. (6) The adverse effect of chemo radiotherapy includes weight loss, acute and long term effects such as xerostomias, dysphagia and fatigue which significantly affect the quality of life of HNC patients. (7) During radiation there is also a change in the anatomy of the site irradiated and thus lead to alteration in treatment planning.

In the past two decades, radiotherapy for the management of HNC has a substantial shift from 2D radiotherapy to 3D-conformal radiotherapy (3D-CRT) and followed by intensity-modulated radiation therapy (IMRT). (8) During the radiotherapy regimen for HNC, there exists an anatomical change as a result of bodyweight or tumour volume and may lead to under dosage or dose inhomogeneity in target organs and over dosage in organs at risk (OARs). (9) During treatment, the organs like the parotid gland which is more sensitive to radiation might move

closer to the high dose regions and causes increased dose exposure leading to xerostomia. (10)

New imaging modalities such as cone-beam computed tomography (CBCT) elicits setup errors during the treatment days lacking to adjust for intrinsic changes which occur in tumour volume and spatial location as well as in normal tissues. (11) Due to these demerits, adaptive radiotherapy (ART) has been developed, which involves the re-planning of the treatment protocol due to adverse changes such as weight loss or tumour shrinkage at pre-defined intervals throughout radiation. This replanning process aid the radiation plan to adjust according to the tumour and normal tissue anatomy, thus decreasing the dose to sensitive structures. The re-planning process aids the radiation plan to alter as per the changing tumour and normal-tissue anatomy and thus decreasing the dose to sensitive organs such as the parotid gland. In addition, the dose reduction is associated with inhomogeneity and inadequate target coverage. Thus, the ART can be known as anatomy-adapted adaptive radiotherapy (A-ART), given ART is guided by structural changes occurring throughout radiation. Against this backdrop, the present study was carried out to evaluate the dosimetric parameters and clinical benefit in adaptive radiotherapy for the management of locally advanced head and neck cancers.

Materials And Methods

This was a prospective interventional study conducted among the 10 histologically proven cases of head and carcinoma with stage III-IV (locally advanced). All the patients received definitive conformal radiation therapy to the head and neck region.

All biopsy-proven locally advanced head and neck cancer planned for definitive chemo-radiation and patients with ECOG≤ 2 were included in the study.

Patients with a history of previous irradiation, metastatic disease, recurrent disease, post-operative head and neck cancer, ECOG>2 or received induction chemotherapy were excluded from the study.

After informed consent, all patients underwent pre-treatment evaluation, including detailed clinical examination, lab investigations (complete blood picture, liver and renal function tests), diagnostic contrast enhancement computed tomography of head and neck, and chest x-ray.

Simulation CT was taken with SOMATOM DEFINITION AS. A planning CT was taken in supine position with intravenous contrast agents is acquired with 3mm slice thickness from the vertex to the carina. A thermoplastic head and shoulder mask with five fixation points is used. Images were transferred electronically to MONACO (version 5.1) for contouring and planning. Contouring of lymph nodes was done according to Consensus guidelines. Gross tumour volume (GTV) corresponded to the primary tumour along with involved lymph nodes. Clinical target volume 70 Gy (CTV70) was given a margin to GTV to encompass the probable areas of the microscopic spread of disease, which was adjusted to exclude air cavities and bone mass without evidence of tumour invasion. CTV54 corresponded to the adjacent lymph nodal sites, while CTV50 corresponded to the next echelon of the nodal site to be treated prophylactically depending on the clinical situation. GTV, CTV70, CTV60, CTV54, along with respective PTVs and all organs at risk were manually delineated on each CT slice incorporating information from MRI, PET-CT if already done. Adding a 5mm margin around the CTVs generated the PTVs. PTV expansion was limited to 4 mm from the skin surface to avoid the build-up region and to limit skin toxicity. All IMRT plans were generated using MONACO. Nine coplanar 6MV photon beams were employed with dynamic MLC (Multileaf collimator) IMRT(Intensity Modulated Radiation Therapy) technique. The prescribed dose was 70 Gy/33# to PTV1, 60 Gy/33# to PTV2, and 54 Gy/33# to PTV3. The maximum dose within the PTV was 110% (D2%). The minimum PTV volume covered by the 95% isodose line was 95%. The collapsed cone convolution/superstition algorithm was used for dose calculation.

Dose constraints were set according to the QUANTEC recomm endations. All patients underwent IMRT using a total dose of 70 Gy/33# with a simultaneous integrated boost technique and concomitant chemotherapy was decided according to the patient criteria.

Dose-volume parameters will be obtained from the Dose Volume Histogram of Treatment Planning System (Monaco) using Analytical Anisotropic Algorithm present in our department.

During the treatment, a replanning CT was taken for each patient at 21st fraction according to the same modalities as the first CT, except for intravenous contrast agents (not systematically used, particularly in patients receiving cisplatin-based chemotherapy.

In case of complete response, initial macroscopically involved areas are included in the CTV70 which was adjusted to exclude any air cavities and bone mass without evidence of initial tumour invasion.

Anatomical variations (between CT0 and 4 weekly CT) were characterised by variations in CTV70 and parotid gland volume, in the distances between parotid glands and CTV70 and in the thickness of the neck (at the level of the geometrical centres of the parotid glands).

All patients in this study were followed up weekly by clinical examination during RT and post RT every month till 3 months and then every 6-8 weekly. During follow up worst grade of the above-mentioned toxicities was recorded.

The original treatment plan (Plan 1) was overlaid on the new image set using the matched isocenter and predefined bony anatomy. The dose distribution was recalculated, and dose-volume histograms were generated (plan 2). A new plan was generated with reoptimization using the same optimization parameters (plan 3). The 3 plans were then compared using predefined parameters.

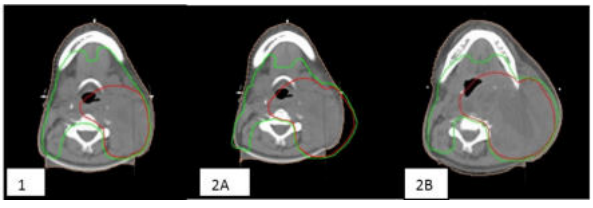

Figure 1. Baseline Contour Of Locally Advanced Ca Nasopharynx

Figure 2.
A. Contour Overlay On Mid Therapy Image
B. Contour Showing Volume Changes During The Course Of Radiation Therapy

Statistical Analysis

The data was coded and entered into a Microsoft Excel spreadsheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. Descriptive statistics included computation of percentages, means and standard deviations. The data were checked for normality before statistical analysis using Shapiro–Wilk test. Quantitatively, parameter data were analyzed using t-test like unpaired and paired while nonparametric data were analyzed using Wilcoxon signed-rank test and Mann–Whitney U-test.

RESULTS

Patients enrolled in this prospective study were ten in number and the study was conducted between December 2020 to May 2021. All patients had completed treatment without any interruptions. Four patients had locally advanced nasopharyngeal cancer, four patients had oropharyngeal cancers and another two patients had hypopharyngeal cancers. The mean age of the patient is 41.8 years. All patients were treated with IMRT.

Dosimetric Analysis:

The 3 plans were compared using predefined parameters

Comparison between plan 1 and plan 2:

There was significant difference in the planning target volume (PTV) among the plan 1 and plan 2, at D99 (p=0.007), D95 (p=0.002), Dmax (p=0.001), V95 (p=0.002) and V93 (p=0.004). Meanwhile, there was no significant difference for Dmean between plan 1 and plan 2 (p=0.444). Further, there was no significant difference for the right parotid, left parotid for Dmean and V26. The spinal cord for Dmax (p=0.156) and D1cc (p=0.068) was also found to be non-significant between plan 1 and plan2 but the dose received is higher in plan 2 than in plan 1. The brain stem for Dmax (p=0.025), D1cc (p=0.013) and D1% (p=0.03) were also found to be significant between plan 1 and plan 2. The results were shown in table 1.

Table 1: Dosimetric effect on PTV and organs at risk between plan 1 and plan 2

	Variable	Plan1: Mean (SD)	Plan 2: Mean(SD)	Mean difference (SD)	95% CI of mean	Significance (P)
PTV	D99	98.68 (1.87)	89.64 (8.44)	9.03(8.21)	3.16 to 14.91	0.007
	D95	101.12 (65)	98.62(2.2)	2.51(1.9)	1.14 to 3.87	0.002
	Dmax	110.79 (1.12)	113.44 (1.99)	-2.65 (1.67)	-3.85 to -1.45	0.001
	Dmean	107.79 (1.25)	108.05 (1.79)	-0.26 (1.01)	-0.98 to 0.47	0.444
	V95	99.854 (0.13)	97.83(1.5)	2.02(1.49)	0.95 to 3.1	0.002
	V93	99.93 (0.08)	98.4(1.26)	1.54(1.25)	0.65 to 2.44	0.004
Rt Parotid	Dmean	63.15 (14.07)	68.69 (20.72)	-5.54 (14.69)	-16.05 to 5	0.263
	V26	67.20 (21.74)	74.96(22.53)	-7.75 (17.76)	-20.46 to 4.95	0.201
Lt Parotid	Dmean	63.09 (14.42)	68.2 (16.15)	-5.11 (7.35)	-10.37 to 0.14	0.055
	V26	69.756 (23.39)	77.97 (17.86)	-8.21 (17.34)	-20.62 to 4.19	0.168
Spinal cord	Dmax	58.96 (6.88)	68.76 (21.51)	-9.8(20)	-24.09 to 4.51	0.156
	D1cc	45.83(7.7)	57.81 (20.90)	-11.98 (18.27)	-25.05 to 1.08	0.068
Brainstem	Dmax	65.16 (23.59)	70.51 (25.28)	-5.35 (6.29)	-9.85 to -0.85	0.025
	D1cc	48.11 (24.10)	54.71(28.53)	-6.6(6.73)	-11.41 to -1.78	0.013
	D1%	56.95 (24.3)	62.33(27.4)	-5.38(6.6)	-10.11 to -0.644	0.03

D99: dose received by 99% of the target volume, Dmax: maximum dose received; Dmean: mean dose received; V95: volume receiving 95% of the prescription dose; V26:volume of the parotid gland receiving 26 Gy; D1cc: Dose received by 1mL of the volume; D1%: dose received by 1% of the volume; PTV: Planning target volume.

Comparison Between Plan 2 And Plan 3:

When comparing the dosimetric data between the plan 2 and plan 3 there was a significant difference for planning target volume (PTV) at D99 (p=0.004), D95 (p=0.002), Dmax (p=0.003), V95 (p=0.001) and V93 (p=0.004). Meanwhile, there was no significant difference for Dmean between plan 2 and plan 3 (p=0.744). Further, there was no significant difference for the right parotid, left parotid for Dmean and V26. The spinal cord for Dmax (p=0.036) and D1cc (p=0.0440) was also found to be significant between plan 2 and plan 3. Further, there was no significant change in the brain stem between plan 2 and plan 3 for Dmax (p=0.934), D1cc (p=0.889) and D1% (p=0.833). The results were shown in table 2.

Table 2: Dosimetric effect of replanning on PTV and OARs (Plan 2 and Plan 3)

	Variable	Plan 2: Mean (SD)	Plan 3: Mean (SD)	Mean difference (SD)	95% CI of mean	Significance (P) (Wilcoxon)
PTV	D99	89.64 (8.4)	98.65 (2.2)	9.01(7.55)	3.61 to 14.4	0.0040
	D95	98.62(2.2)	100.99(0.82)	2.37(1.78)	1.09 to 3.64	0.0020
	Dmax	113.44 (2)	111(0.93)	-2.44 (1.96)	-3.84 to -1.04	0.0030
	Dmean	108.05 (1.8)	107.91 (1.83)	-0.14(1.3)	-1.07 to 0.79	0.7440
	V95	97.83 (1.53)	99.80(0.25)	1.97(1.38)	0.98 to 2.96	0.0010
	V93	98.38 (1.26)	99.83(0.34)	1.45(1.1)	0.66 to 2.23	0.0020
Rt Parotid	Dmean	68.69(20.71)	67.76 (14.25)	-0.93 (16.99)	-13.08 to 11.23	0.8670
	V26	74.95 (22.52)	77.42(17.9)	2.46 (22.17)	-13.41 to 18.31	0.7350
Lt Parotid	Dmean	68.2 (16.15)	68.57 (17.45)	0.37(9.42)	-6.38 to 7.11	0.9050
	V26	77.97(17.86)	78.565 (18.92)	0.59(12.7)	-8.49 to 9.68	0.8850
Spinal cord	Dmax	68.76 (21.51)	54.97 (11.54)	-13.79 (17.67)	-26.44 to -1.14	0.0360
	D1cc	57.81 (20.9)	43.36(8.4)	-14.45 (19.5)	-28.40 to-4.97	0.0440
Brainstem	Dmax	70.51 (25.28)	70.9(26.6)	0.39 (14.54)	-10.01 to 10.79	0.9340
	D1cc	54.71 (28.53)	55.73 (26.26)	1.02 (22.56)	-15.11 to 17.15	0.8890
	D1%	62.33 (27.4)	63.67 (26.75)	1.34 (19.56)	-12.65 to 15.33	0.8330

D99: dose received by 99% of the target volume, Dmax: maximum dose received; Dmean: mean dose received; V95: volume receiving 95% of the prescription dose; V26:volume of the parotid gland receiving 26 Gy; D1cc: Dose received by 1mL of the volume; D1%: dose received by 1% of the volume; PTV: Planning target volume.

Volumetric Changes

The volumetric data for planning (CT1) and replanning (CT2) were shown in Fig 3. There was a marked reduction in volume in CT2 as compared to CT1 in terms of gross tumour volume, clinical target volume (CTV), planning target volume (PTV), right and left parotid.

All mean target volumes showed reductions during radiation therapy (Fig 3A). Mean GTV volume reduction in the primary (GTVp) was 12.6 mL while mean GTV volume reduction in the node (GTVn) was 24.5mL. The corresponding mean change in CTV70 was 53.71 mL while the corresponding change in PTV70 was 17.47 mL.

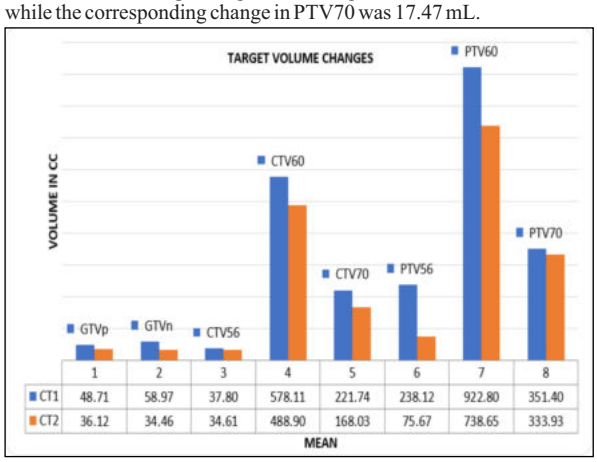

Fig 3A: Mean target volume change during RT. CT 1= Original CT plan; CT2 = Replanning CT plan

The mean volume change for the right and left parotid glands were 5.94 mL and 5.49 mL, respectively as shown in Figure 3.

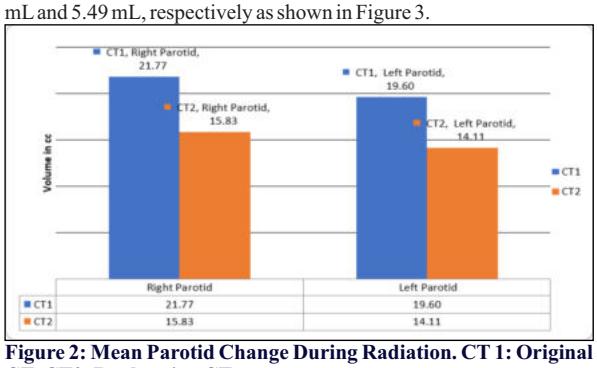

Figure 2: Mean Parotid Change During Radiation. CT 1: Original CT; CT2: Replanning CT

DISCUSSION

The present paper was done for the evaluation of the dosimetric implications of changes in the anatomy and the effectiveness of ART in adults receiving external beam radiation therapy for tumours in the head and neck region. In the present, there was a significant change in the target and normal tissue volumes during the treatment course, post

two weeks after the initiation of radiation therapy which is in line with the earlier reports.(13,14)

The vital problems faced by the Radiation Oncologists during replanning of ART are the signs of change in GTV and CTV during the treatment process. The original image acquisition and replanning CT scans were performed on the same dedicated CT simulator. This leads to a uniform pattern of dosimetric evaluation and cumulative dosimetric comparison between various plans in the event of the treatment course.

The changes in the GTV was documented based on the replanning CT scan images but the CTV was not modified, except in the areas where CTV extended beyond the body contours or into the body cavities, which were unlikely to harbour microscopic disease. (15) Ahn et al had modified the original CTVs to account for changes in the patient anatomy (spinal cord, brainstem, mandible, parotids) or positioning changes which are similarly done in the present study. The target volumes were delineated by International Commission on Radiation Units and measurements nomenclature. The PTV was similarly grown with margins around the CTV as was done in the original planning scan.

In our study, 2 sets of images (original and replanning) were fused manually using the software available in ELEKTA to get the best possible match between 2 sets of images. Significant tumour shrinkage was noted in all the patients that altered the body contour. There is a significant impact on the final dose distribution due to the changes in the patients' anatomy during treatment.

It was observed that when the original plan was applied on the replanning CT images, there is a significant increase in the dose to the spinal cord which was more due to the positional errors rather than the tumour shrinkage. However, we eliminated the setup errors during CT-CT fusion, making sure that the setup errors were due to anatomic changes in the tumour and body contour and not because of patient positioning errors. The original and replanning (nonoptimized) scan dosimetric analysis showed variations in the doses to the target volumes and various OARs, most of them were statistically significant (parotid Dmean, spinal cord D1cc, brainstem Dmax, D1cc, D1%). It is seen that there is an increase in the dose to the spinal cord in patients with large cervical nodes that has a response to radiation, hence showing significant changes in the patient's anatomy in the cervical region. The variation differs in patients based on the initial nodal volume/size and the response to therapy. Thus it is important to evaluate the benefit of replanning based on individual data and not on patients' groups treated similarly. We noticed that the PTV coverage and doses to the OARs like the spinal cord with replanning had shown improvement. The body contours of all the 10 patients in the study are altered. The mean Dmax of the spinal cord in the non-optimized plan increased from 58.96 Gy to 68.76 Gy with a mean difference of -9.8% (95% CI=-24.09 to 4.51; p=0.156). The mean dose to 1ml volume (D1cc spinal cord) was also increased from 45.83% to 57.81% (95% CI=-25.05% to 1.08%; P=0.068). We had noted improvement in PTV coverage and decreased doses to the spinal cord with replanning. But the dose to the parotids and the brainstem had slightly increased but insignificant. The findings from the study had suggested that ART can be useful in selected patients.

In the present study, the thermoplastic mould had to be remade in all the patients because of significant loosening which had led to significant changes in the body contour. The average time taken was 72 hrs from remaking of moulds to replanning/optimization and restarting treatment.

In the present prospective study, the number of patients' sample is small and the histological subtypes of the tumour treated are also heterogenous highlighting the importance of ART for tumours within the H&N cancers.

CONCLUSIONS

Replanning during radical radiation therapy for locally advanced head and neck cancer is effective in selected patients with tumours having large volumes. During treatment, there are significant changes in the contours of the body of the patients leading to loosening of the immobilization devices. This study demonstrates that during radiation there is a gross change of volumes in locally advanced head and neck cancers and thus adaptive radiation therapy plays a pivotal role in intensity-modulated preventing higher dose to OARs viz. spinal cord and parotid glands.

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