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# Impact of head and neck intensity modulated radiation therapy on CT numbers of primary and nodal Gross tumour volume

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## Abstract

**Introduction:** CT number (CTN) for the gross tumour volumes (GTV) can change with radiation therapy which could be an early indicator for radiation response. This study investigates the correlation of radiation induced changes in volume and CTN in GTV of primary and nodal tumour during the course of intensity modulated radiation therapy (IMRT) in head and neck cancers (HNC).

**Materials and Method:** Re-CT scans were acquired at 4 weeks for 71 patients with stage II- IVb HNC treated with chemoradiation. The changes in volumes and CTN of the GTV primary and GTV node at 4 weeks of radiation were observed. Pearsons's correlation were used to assess any correlation between CTN change and volume reduction of the GTVs.

**Results:** The volumes of the GTV Primary and GTV Node were reduced during the course of the radiation therapy after 4 weeks with mean volume shrinkage of 26.30±7.66($p<0.0001$) and 32.09±37.2($p<0.04$) respectively and the mean CTN reduced by 2.50±5.4 and 1.79±4.12HU's respectively. The CTN and GTV volume decreases were found to be positively correlated (GTVP >GTV N) though the relationship is weak.

**Conclusion:** The CTN changes in GTV P and GTV N during delivery of radiation for HNC is measurable and are patient specific. The volume reduction is observed more in GTV N where as CTN reduction is noticed in both GTVs with a reasonable correlation between the mean CTN and volume reductions in GTVs.

**Keywords:** Head and neck cancer, CT number change, IMRT, Gross tumour volume.

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## Introduction

The standard treatment of head and neck cancers is intensity modulated radiation therapy (IMRT) with image guidance.[1-9] Image guidance is used to account for interfractional variations for setup uncertainty as well as anatomical changes. The changes in the tumour volumes and organ at risk (OAR), constitute the anatomical changes which accounts for the major interfractional variations that occur during the delivery of radiation course for head and neck cancers (HNC).[1,10] However image guided radiation therapy cannot completely account for these changes. Hence adaptive radiotherapy has been introduced[11,12] where the treatment plan is revised and then delivered based on changes in tumour and organ at risk anatomy.[13,14] The timing of adaptive replaning during the course of RT delivery is still an unsolved issue. Brown et al considered replanning at week 4 of radiation therapy for oropharyngeal cancer patients with neck nodes.[15]

CT number (CTN) for the GTV P and GTV N can change after radiation therapy. The change in CTN could be an early indicator for radiation response and local control.[16-19] Howells et al.[18] reported the decreased normal liver tissue density to be correlated with RT dose with stereotactic body radiation (SBRT) in liver cancer. Palma et al quantitatively analysed the decrease in normal lung density in SBRT lung tumours and observed the relation with CTN.[17] Diot et al reported the change in CTN with relation to radiation dose in SBRT lung.[16] Mayer et al found the CT number reduction and its association with local control in lung cancer.[19]

In our study, we investigated the changes in CT number for gross tumour volume primary and nodes according to the re-CT scan done at 4 weeks/20 fractions in HNC patients treated with chemoradiation with IMRT.

## Materials and Method

The study was carried out on pathologically proven HNC patients coming to radiation department in our institute from June 2012 to July 2016. 72 patients included in the study were staged according to TNM staging system; AJCC, 7th edition. Contrast enhanced CT scan were acquired using GE 16 slice spiral ELITE CT scanner with 2.5mm slice thickness from base of skull to upper mediastinum.

IMRT plans with seven beams with MLC of 40 pairs with 1cm width at isocenter were optimised. Dose calculation was based on anisotropic analytical algorithm (AAA) (version 13.0.26) with the intent of predicting the delivery dose to the patient. The optimisation was based on dose constraints as per RTOG guidelines with respect to tumour coverage and minimization of dose to OAR. IMRT plans were generated and approved for each patient on treatment

planning system ECLIPSE version 8.6,13 (Varian medical system, Palo Alto, CA). For all patients, gross tumour volume (GTV) and nodal disease were treated with 6 MV varian DBX to a dose of 66-70 Gy in 33-35 fractions with microscopic disease addressed with 50-54 Gy of radiation, along with 4-6 cycle of concurrent cisplatin based chemotherapy ±targeted therapy.

A repeat CT scan was acquired at end of 20$^{th}$ fraction/4 weeks. The GTV P and GTV N were contoured into the repeat CT images to obtain 3-dimensional tumour volumes, with an effort to minimise the variation in contour delineation. The delineation uncertainty should not affect the observed results, since we are focusing at the changes in the mean CTN's only. Changes in the GTV of tumour and the nodes between these two CT images were analyzed. TVRR, defined as the percent (%) reduction of the GTV in relation to the pre-RT GTV, where TVRR=(Pre-RT GTV–Mid-RT GTV)/Pre-RT GTV was obtained.

**Data analysis:** ECLIPSE version 13.0.26, planning software were used to analyse the generated contours of the GTV P and GTV N. The CTN (in HU) in every voxel inside the contoured structure were specified. The mean CTN, maximum CTN and standard deviation of the GTVs were calculated. Dose volume calculation model AAA.13.0.26 were used to measure the volume of both GTVs. -400 HU was a reasonable cut off point to distinguish tissue and air in head and neck region.[6] CTN below -400 HU were excluded from data analysis .The changes in the tumour volume, mean and max CTN of GTV P and GTV N at 4 weeks of radiation treatment were also analysed. Two tailed Pearson correlation analysis was carried out to assess the correlations between the CTN change and GTV volume change.

## Results

A total of 71 patients diagnosed with head and neck cancer receiving treatment at our institute were included in the study.

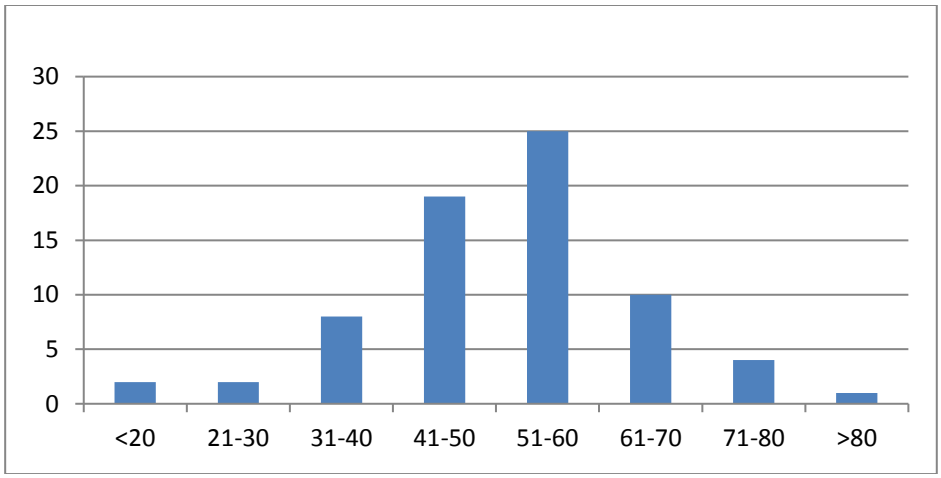


**Fig. 1: Age Distribution**

Among the 71 patients studied, 25 (35%) patients were in an age group of 51-60 years, 19 (27%) between 41-50 years. Of the total patients, 56 (78%) were males and 15 (22%) were females. The ratio of males: females =3.54:1.

Of the 71 patients studied, 25(35%) were diagnosed of carcinoma oropharynx, 20 (28%) carcinoma hypopharynx, 16 (22.5%) carcinoma oral cavity, 10 (14%) carcinoma nasopharynx and 1 patient with metastates of unknown origin with neck nodes.

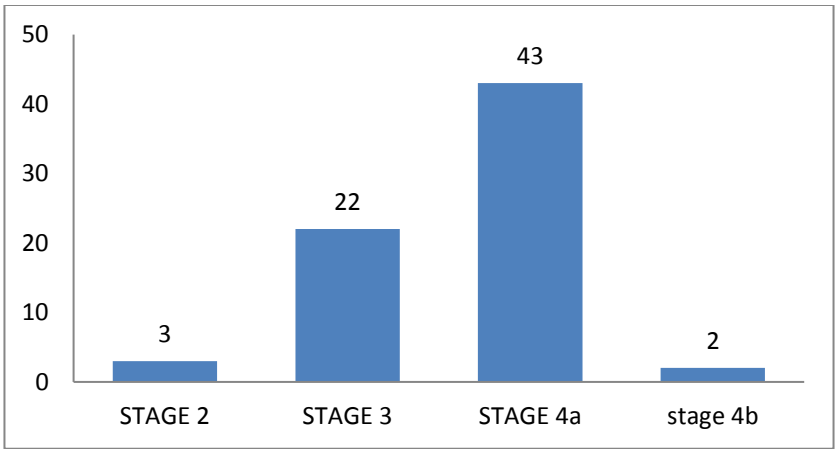


**Fig. 2: TNM staging of Head and Neck Tumours**

Of the 70 patients staged as per TNM staging, 43 (61%) patients were stage 4a, 22 (31%) were stage 3, 3 patients were stage 2, 2 patients were staged 4b. One patient was with unknown primary with neck nodes (Fig. 2).

**Treatment Plan (Table 1):** Of the 71 patients studied, 65 patients (91.5%) received 70 Gy/35 fractions and 6 patients (8.5%) received 66Gy/33 fractions of radical radiation therapy.

**Table 1: Treatment Plan**

| Treatment Plan | Number | Percentage |
|---|---|---|
| Cetuximab + cisplatin + radiation (70Gy/35#) | 3 | 4.22 |
| Nimotuzumab + cisplatin +radiation (70Gy/35#) | 3 | 4.22 |
| Paclitaxel + cisplatin + radiation (70Gy/35#) | 1 | 1.40 |
| Docetaxel + cisplatin + radiation (70Gy/35#) | 1 | 1.40 |
| Cisplatin+ radiation (70 Gy/35#) | 57 | 80.28 |
| Cisplatin+ radiation (66 Gy/33#) | 6 | 8.45 |
| Total | 71 | 100 |

For the 70 patients with GTV P, the dose $D_{mean}$ (Gy) was 70.11 Gy. $D_{mean}$ (Gy) for GTV N was 71.11 Gy. The mean dose for ipsilateral parotids for all the 71 patients was 29.88 Gy. The mean dose for contralateral parotids for all the 71 patients was 25.42 Gy. The mean dose for spinal cord was 22.93 Gy. (Table 2).

**Table 2: Dosimetric analysis of tumour and organ at risk**

| Volume/Organ at risk | $D_{mean}$ (Gy) |
|---|---|
| GTV primary | 70.90 |
| GTV node | 71.11 |
| Ipsilateral parotid | 29.88 |
| Contralateral parotid | 25.42 |
| Spinal cord | 22.93 |

For all the 71 patients in the study, the mean volume reductions at mid-RT (+/- SD) for GTV primary and GTV node were 26.30±7.66 ($p<0.0001$) and 32.09±37.2$cm^3$ ($p<0.04$) respectively. The mean volumes of pre-RT and mid-RT GTV P were 56.69$cm^3$ (±12.16 $cm^3$) and 26.7 $cm^3$(±7.55$cm^3$), respectively. The mean Tumour Volume Reduction Rate (TVRR) relative to pre-RT baseline was -46.38%. The mean volumes of pre-RT and mid-RT GTV N were 48.28$cm^3$ (±41.91 $cm^3$) and 16.18 $cm^3$(±9.28$cm^3$), respectively. The TVRR relative to pre-RT baseline was -66.48%. There is a detectable changes in CTN seen from the re-CT scan acquired after 20 fractions in most of the patients, while there is significant anatomical changes in the volumes of both GTV P and GTV N. The mean CTN changes in GTV P and GTV N were 2.50±5.4 and 1.79±4.12 HU respectively. Changes noted are highly patient specific. Out of the 70 patients with clinically and radiologically detectable GTV Primary, 12 patients had a significant reduction in mean CTN of GTV P of more than 20HU with 50 patients showing a varied moderate reduction in mean CTN with a total of 88.57% patients showing definitive reduction in mean CTN. Similarly, around 8 among the 43patients with clinically and radiological proven neck nodes GTV N had a significant reduction in mean CTN of more than 20HU with a 67% of patients showing mild to moderate reduction in mean CTN with a total of 86.05% patients showing definitive reduction in mean CTN. It is also observed that in overall just less than 10% of the patients had a marginal increase in the mean CTN noted in both GTV P and GTV N. It is observed that the mean CTN reduction is observed slightly more in GTV P than in GTV N. The max CTN changes in GTV P and GTV N were 36.17±108.2 and 90.41±62.2 HU($p<0.002$) respectively. There is a positive correlation observed between the mean CTN reduction and relative volume reduction for GTV P with a pearson`s correlation coefficient 0.136 even though the relationship is weak and with a coefficient of

determination 0.0187 (Fig. 3). Similar positive correlation is observed between the mean CTN reduction and relative volume reduction for GTV N with a pearson's correlation coefficient 0.073 (Fig. 4) and with a coefficient of determination 0.0054 .However there is no correlation observed between the max CTN reduction and relative volume reduction for GTV N with a pearson's correlation coefficient -0.0693 (Fig. 5) and with a coefficient of determination 0.0048.

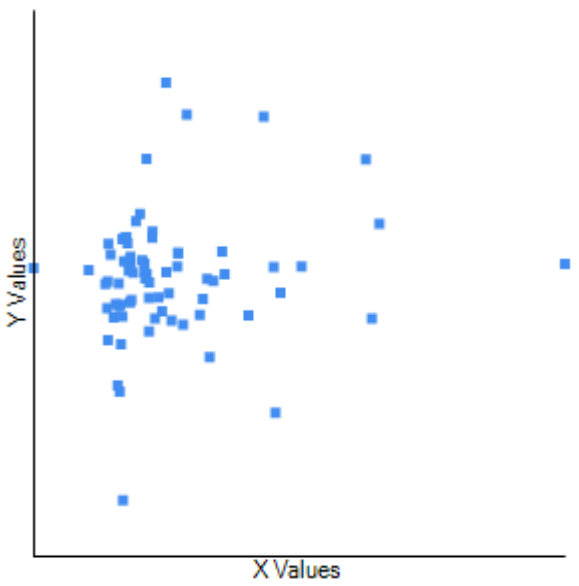


**Fig. 3: Correlation of relative volume reductions (X Values) and mean CTN reductions (HU) of GTV Primary**

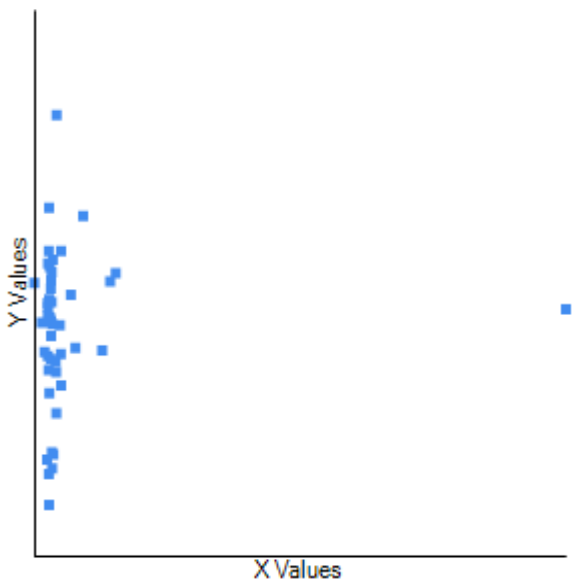


**Fig. 4: Correlation of relative volume reductions (X Values) and mean CTN reductions (HU) of GTV Node**

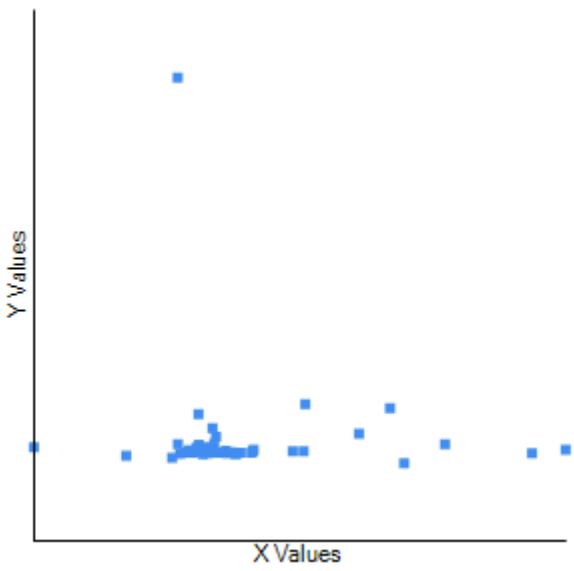


**Fig. 5: Correlation of relative volume reductions (X Values) and max CTN reductions (HU) of GTV Node**

## Discussion

Head and neck (H&N) cancer patients undergo anatomical change throughout the radiation treatment. Adaptive radiotherapy (ART) addresses the impact of this change on the planned dose distribution. Browne et al.[15] concluded that for H&N patients with neck nodes receiving definitive chemoradiotherapy, re-planning may be considered at week 3 for NPC patients and in

week 4 of treatment for OPC patients. Yang et al[20] reported that timing of ART for HNC patients should be in the fourth or fifth week of treatment to facilitate adequate volumetric response to radiation while preserving adequate treatment time for re-planning. The time for re-CT in our study is 4 weeks /20 fractions. Significant tumour volume regression observed in this study during around mid-treatment with radiation are comparable with studies done previously.[1,10,21] Barker et al[1] reported GTV decrease throughout the course of fractionated radiation at a median rate of 0.2 $cm^3$ per treatment day (range,0.01-1.95 $cm^3$/day) and in terms of the percentage of the initial tumour volume, the GTV s decreased at a median rate of 1.8% per treatment day (range, 0.2-3.1%/day). Similar findings are observed in this study with the mean volume reductions(+/- SD) for GTV primary and GTV node were 26.30±7.66 ($p<0.0001$)and 32.09±37.2$cm^3$ ($p<0.04$) respectively which corresponds to 2.3% and 3.32% volume reduction per day respectively. The mean Tumour Volume Reduction Rate (TVRR) relative to pre-RT baseline for GTV P was - 46.38% (0.4638) and TVRR relative to pre-RT baseline for GTV N was -66.48% (0.6648). Yang et al[20] showed the mean TVRR of 0.43 in GTV P for oropharyngeal cancer and 0.33 in GTV P for hypopharyngeal cancer over 4-5 week period. Hyabin lee et al[22] reported the mean TVRR relative to pre-RT baseline in nasopharyngeal cancer as –41.9% (0.419). In this study, we not only note the TVRR to be comparable to that of the above studies, but also observe that the nodal regression was more than the primary tumour reduction.

The mean CTN changes observed in both the GTVs during the course of radiation are highly patient specific. Though around 90% of patients showed reduction in the mean CTN of the GTV P and GTV N, a substantial change were observed only in around 20%. Similar reports from Mei Feng et al[23] and Shouping Xu et al[24] confirm that the CTN changes are highly patient specific. The tumour and normal structure change in mean CTN during and after radiation are reported in various studies. Xu et al.[25] noticed reduction in mean CTN in GTV and parotid glands during the delivery of fractionated radiotherapy for nasopharyngeal cancers. Mayer et al[19] observed a mean CTN reduction of -3 to -36HU in lung tumor volumes in patients treated with conventional fractionation dose upto 66.6 Grays. De et al.[26] reported the CTN change with radiation dose observed in lung tumours were highly patient specific and ranged from 0-10HU/Gy. Howell et al[18] observed the reduced CTN in post SBRT normal liver after liver irradiation. Thalacker et al[27] observed the reduction of CTN of white matter by 5 HU after brain irradiation. Mei Feng et al[23] reported a decrease in mean CTN in tumour during the course of radiation in HNC with a fair correlation between CTN reduction and radiation dose for a subset of patient but also reported that the correlation between volume reductions and CTN reductions in the GTV to be weak. In our study too we observe a positive correlation between the mean CTN reduction and relative volume reduction for GTV P and for GTV N even though the relationship is weak .However there is no correlation observed between the max CTN reduction and relative volume reduction for GTV N. The patient specific CTN changes observed in the GTV in this study may be related to the radiation response of the individual patient, as the doses received at the timing of re-CT scan were the same for all the patients. The mechanism behind this CTN change is still unclear. Yue Cao et al[28] reported that an increase in blood volume of the primary tumour volume early in the course of RT(after 2 weeks of RT) in HNC patients with local control (median change, 5.1 ml/100 g) .This increase is significantly higher than the change in blood volume of patients with local failure (median change, 1.0 ml/100 g). This study suggested that an increase in local blood supply, thereby potentially a source of improved tumour oxygenation, may be an early positive indicator for predicting the therapeutic response at the primary tumor site and the disease prognosis of HNC patients. Truong et al[29] reported that the pre-treatment tumour blood flow and the capillary permeability were significantly higher in patients who achieved loco-regional control than in patients with treatment failure. Based on these studies, we infer that the CTN reductions in the GTV observed might be as a result of the increased tumour blood volume .As the radiation dose increases, there is shrinkage of GTV, whereas there is an increase in the tumour blood volume which might make the tumour appear hypodense, resulting in the reduction in the CTN of the GTV. The radiation induced CTN changes may be recognised as an early indicator for radiation response for a subset of patients. If this indicator is verified and the mechanism behind is explored, the CTN change can potentially be used as a complimentary indicator to be added or replace the dosimetric indicators currently in use in adaptive radiotherapy in HNC.

## Conclusion

The GTV nodal volume regression was more than the GTV primary tumour volume reduction .The CTN can be reduced in both the tumour volumes (GTV P slightly more than GTV N) during the midway course of radiation therapy for HNC. There is a reasonable correlation between the mean CTN reductions and volume reductions in GTV P and GTV N with a correlation stronger with GTV P than with GTV N. These observations of the CTN changes are highly patient specific and may be used as an indicator to trigger adaptive radiation therapy for HNC.

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