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Radiation-induced changes in volume and CT number of gross tumour volume and parotid glands during the course of IMRT for head and neck cancers

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ABSTRACT

Introduction. The CT number (CTN) for tumours and organs at risk can change with radiation therapy, which can be an early indicator for radiation response. This study investigates the correlation of radiation-induced changes in volume and CTN in gross tumour volume (GTV) and parotid glands (PG) during the course of intensity-modulated radiation therapy (IMRT) in head and neck cancers (HNC).

Materials and methods. Re-CT scans were acquired at four weeks for 71 patients with stage II IVb HNC treated with chemoradiation. The changes in volumes and CTN of the GTV primary, GTV node, and PG at four weeks of radiation were analysed. Pearson's correlation was used to assess any association between CTN change and volume reduction of the GTVs and PGs.

Results. The volumes of the GTVs and the ipsilateral PG and contralateral PG were reduced during the course of the radiation therapy after four weeks with mean volume shrinkage of 26.30 ± 7.66 ($p < 0.0001$), 32.09 ± 37.2 ($p < 0.04$), 8.38 ± 1.61 ($p < 0.0001$), and $9.10 \pm 1.81 \text{ cm}^3$ ($p < 0.0001$), respectively, and the mean CTN reduced by 2.50 ± 5.4 , 1.79 ± 4.12 , 1.90 ± 3.57 , and 1.99 ± 3.54 HUs, respectively. For GTVs, the CTN and GTV volume decreases were found to be positively correlated, but the relationship was weak. However, no noticeable correlation was observed between the CTN change and the volume change in both PGs.

Conclusions. The CTN changes in GTVs and PGs during delivery of radiation for HNC are measurable and patient specific. The CTN can be reduced in GTVs and PGs with a reasonable correlation between the mean CTN and volume reductions in GTVs, but with no correlation with PGs.

Key words: head and neck cancer, CT number change, IMRT, gross tumour volume, parotid glands

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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 that account for the major interfractional variations that occur during the delivery of

a 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] in which the treatment plan is revised and then delivered based on changes in tumour and organ at risk anatomy [13, 14]. The timing of adaptive re-planning during the course of RT delivery is still an unsolved issue. Brown et al. considered re-planning at week 4 of radiation therapy for oropharyngeal cancer patients with neck nodes [15].

The CT number (CTN) for the tumour and organs at risk 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 that decreased normal liver tissue density 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 in 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 and the parotid glands according to the re-CT scan done at four weeks/20 fractions in HNC patients treated with chemoradiation, and examined how these changes are associated with the anatomical changes observed.

Materials and methods

The study was carried out on pathologically proven HNC patients coming to the radiation department in our institute from June 2012 to July 2016. The 72 patients included in the study were staged according to TNM staging system, AJCC, 7th edition. Immobilisation was done using thermoplastic masks that were custom made to fit the individual patients. The mask was attached to the base plate to fixate the patient and serve as a head support. Contrast-enhanced CT scans were acquired using GE 16-slice spiral ELITE CT scanner with 2.5-mm slice thickness from base of the skull to upper mediastinum.

IMRT plans with seven beams with MLC of 40 pairs with 1 cm width at isocentre 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 according to RTOG guidelines with respect to tumour coverage and minimisation of dose to the organ at risk (OAR). IMRT plans were generated and approved for each patient on the treatment planning system ECLIPSE version 8.6, 13 (Varian medical system, Palo Alto, CA). For all patients, gross tumour volume (GTV P) and nodal disease (GTV N) were treated with 6 MV Varian DBX to a dose of 66–70 Gy in 35 fractions with microscopic disease addressed with 50–54 Gy of radiation, along with 4–6 cycles of concurrent sensitiser with cisplatin \pm targeted therapy.

A repeat CT scan was acquired at end of 20th fraction/4 weeks. The GTV P and GTV N, ipsilateral and contralateral parotid glands were contoured into the repeat CT images to obtain three-dimensional tumour

volumes, with an effort to minimise the variation in contour delineation. The delineation uncertainty should not affect the observed results because we are focusing at the changes in the mean CTNs only. Changes in the GTV of tumour and the nodes between these two CT images were analysed. TVRR, defined as the percentage 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 was used to analyse the generated contours of the GTV and parotid glands. The CTN (in HU) in every voxel inside the contoured structure were specified. The mean CTN, maximum CTN, and standard deviation of the tumour volume GTV and OAR were recorded. Dose volume calculation model AAA.13.0.26 was used to measure the volume of GTV and OARs. -400 HU was a reasonable cut off point to separate tissue and air in the head and neck region [6]. CTNs below -400 HU were excluded from data analysis in GTV. The changes in the tumour volume, mean and max CTN of GTV P, GTV N, and both the parotid glands four weeks after the start of radiation treatment were also analysed.

Results

A total of 71 patients diagnosed with head and neck cancer receiving treatment at our institute were included in the study. Twenty-five (35%) patients were in the age group 51–60 years, and 19 (27%) were in the age group 41–50 years. Fifty-six (78%) were males and 15 (22%) were females. The ratio of male:female was 3.54:1.

Of the total patients studied, 25 (35%) were diagnosed with carcinoma oropharynx, 20 (28%) had hypopharyngeal cancer, 16 (22.5%) had oral cavity cancer, 10 (14%) had nasopharyngeal cancer, and one was diagnosed with metastasis of unknown origin with neck nodes. Of the 70 patients staged as per TNM staging, 43 (61%) patients had stage IVa malignancy, 22 (31%) had stage III malignancy, three had stage II disease, and two had stage IVb disease.

Of the total patients studied, 65 patients (91.5%) received 70 Gy/35 fractions, and six patients (8.5%) received 66 Gy/33 fractions of radical IMRT. Various radiation schedules with sensitiser agents used in the study are listed in Table 1.

Dosimetric analysis recorded for the GTVs and the OARs are listed in Table 2. For the 70 patients with GTV P and GTV N, the doses D_{mean} [Gy] were 70.11 Gy and 71.11 Gy, respectively. The mean doses for ipsilateral parotids and contralateral parotids for all patients were

Table 1. Treatment plan

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

Table 2. Dosimetric parameters of volumes and organs 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

29.88 Gy and 25.42 Gy, respectively. The mean dose for spinal cord was 22.93 Gy.

For all the 71 patients in the study, the mean volume reductions (\pm SD) for GTV primary and GTV node were 26.30 ± 7.66 ($p < 0.0001$) and 32.09 ± 37.2 cm³ ($p < 0.04$), respectively. The mean volume reductions for ipsilateral parotid and contralateral parotid glands are 8.38 ± 1.61 cm³ ($p < 0.0001$) and 9.10 ± 1.81 cm³ ($p < 0.0001$), respectively, which amounts to 36.10% and 38.29% reduction from initial volume, respectively. The mean volumes of pre-RT and mid-RT GTV P were 56.69 cm³ (± 12.16 cm³) and 26.7 cm³ (± 7.55 cm³), 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 cm³ (± 41.91 cm³) and 16.18 cm³ (± 9.28 cm³), respectively. The TVRR relative to pre-RT baseline was -66.48% .

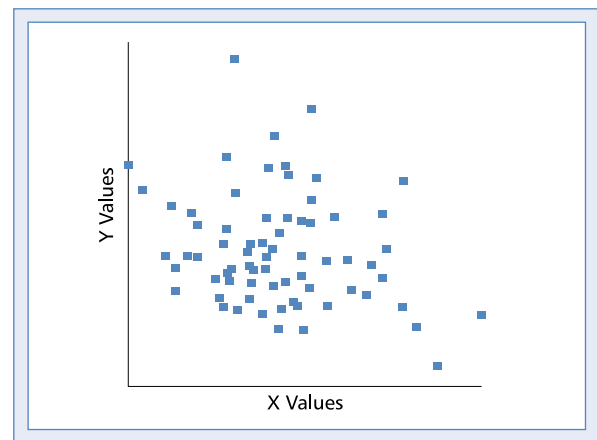
There were detectable changes in CTN seen from the re-CT scan acquired after 20 fractions in most of the patients, while there were significant anatomical changes in the volumes of both GTV and the parotid glands. The mean CTN changes in GTV P and GTV N were 2.50 ± 5.4 and 1.79 ± 4.12 HU, respectively. Similarly, the mean CTN changes in ipsilateral parotid and contralateral parotids were 1.90 ± 3.57 and 1.99 ± 3.54 HU, respectively. The changes noted were highly patient specific. Out of the 70 patients with

clinically and radiologically detectable GTV Primary, 12 had a significant reduction in mean CTN of GTV P of more than 20 HU, with 50 patients showing a varied moderate reduction in mean CTN of GTV P, and with a total of 88.57% patients showing definitive reduction in mean CTN. Similarly, around eight among the 43 patients with clinically and radiologically proven neck nodes GTV N had a significant reduction in mean CTN of more than 20 HU, 67% of patients showing mild to moderate reduction in mean CTN, and with a total of 86.05% patients showing definitive reduction in mean CTN. It is also observed that overall less than 10% of the patients had a marginal increase in the mean CTN noted in both GTV P and GTV N. It was observed that the mean CTN reduction was slightly greater in GTV P than in GTV N.

The correlation of the percentage of volume shrinkage and mean CTN reduction of ipsilateral parotid was 14.85 ± 1.50 and that of contralateral parotid was 14.65 ± 1.44 , showing a mild increased reduction in CTN in ipsilateral parotid; however, in patients with a significant GTV P volume shrinkage, the mean reduction in ipsilateral parotid CTN was greater than the contralateral parotid CTN ($p = 0.07$).

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. Similarly, the max CTN changes in ipsilateral parotid and contralateral parotid were 90.41 ± 62.2 and 32.08 ± 67.50 HU, respectively, the reduction being on similar lines to that seen in mean CTN reduction of ipsilateral parotid.

There was a positive correlation observed between the mean CTN reduction and relative volume reduction for GTV P with a Pearson's correlation coefficient 0.136 although the relationship was weak and with a coefficient of determination 0.0187 (Fig. 1). Similar posi-

**Figure 1.** Correlation of CTN (X Values) and volume (Y Values) reductions of GTV Primary

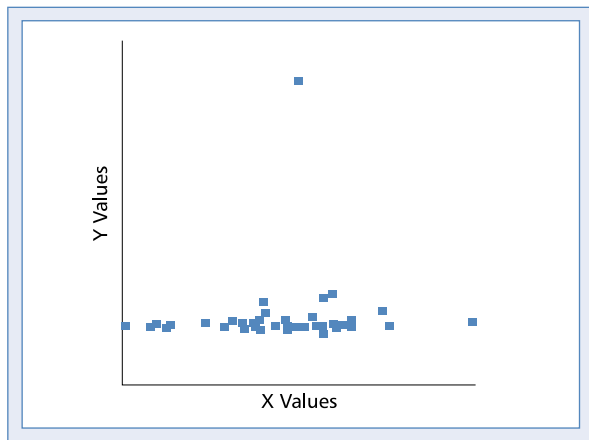


Figure 2. Correlation of CTN (X Values) and volume (Y Values) reductions of GTV Node

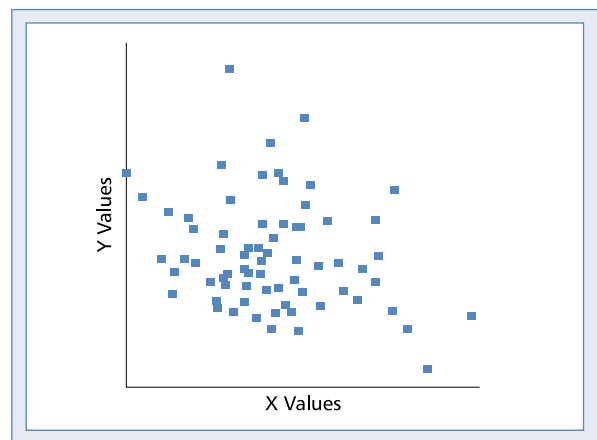


Figure 4. Correlation of CTN (X Values) and volume (Y Values) reductions of contralateral parotid gland

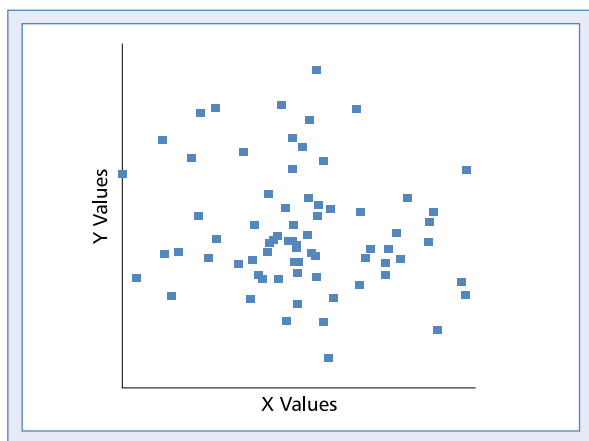


Figure 3. Correlation of CTN (X Values) and volume (Y Values) reductions of ipsilateral parotid gland

tive correlation was observed between the mean CTN reduction and relative volume reduction for GTV N with a Pearson's correlation coefficient of 0.073 (Fig. 2). However, there was no correlation observed between the max CTN reduction and relative volume reduction for GTV N.

There was no correlation observed between the CTN change and the volume change in both the ipsilateral parotid ($p = 0.20$) (Fig. 3) and contralateral parotid glands ($p = 0.04$) (Fig. 4).

Discussion

Head and neck (H&N) cancer patients undergo anatomical change throughout radiation treatment. Adaptive radiotherapy (ART) addresses the impact of this change on the planned dose distribution. Brown et al. [15] concluded that for H&N cancer patients with

neck nodes receiving definitive chemoradiotherapy, re-planning may be considered at week 3 of treatment for nasopharyngeal cancer and at week 4 for oropharyngeal cancer patients. Yang et al. [20] reported that timing of ART for H&N cancer 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 four weeks/20 fractions.

Significant tumour and volume regression of both parotid glands observed in this study around mid-treatment with radiation are comparable with studies done previously [1, 10, 21]. Nishimura et al. [22] reported that the volume of the PGs decreased from 43.1 to 32.0 ml in the third week of a four-week course of IMRT ($p < 0.001$). Fiorentino et al. [23] reported that by the 20th day of treatment, the PGs had shrunk by 30% of the original volume, supporting the hypothesis that, during the third week of RT, a check of the PG volume and/or a re-plan could be indicated, which was in agreement with our research findings showing that the volumes of the ipsilateral and contralateral PGs reduced by 36.1% and 38.2%, respectively, at the end of four weeks.

Barker et al. [1] reported GTV decrease throughout the course of fractionated radiation at a median rate of 0.2 cm³ per treatment day (range 0.01–1.95 cm³/day), and in terms of the percentage of the initial tumour volume, the GTVs decreased at a median rate of 1.8% per treatment day (range 0.2–3.1%/day). Similar findings were observed in this study with mean volume reductions (\pm SD) for GTV primary and GTV node of 26.30 ± 7.66 ($p < 0.0001$) and 32.09 ± 37.2 cm³ ($p < 0.04$), 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 a mean TVRR of 0.43 in GTV P for oropharyngeal cancer and 0.33 in GTV P for hypopharyngeal cancer over a 4–5-week period. Hyabin lee et al. [24] reported the mean TVRR relative to pre-RT baseline in nasopharyngeal cancer as –41.9% (0.419). In this study, we not only noted that the TVRR was comparable to that of the above studies, but also that the nodal regression was more than the primary tumour reduction as the increased tumour nodal vasculature and oxygenation might have determined the volume reduction.

The mean CTN changes observed in both the GTV and the parotid glands 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 was observed only at around 20%. Similarly, the mean CTN of the parotid glands was also patient specific with a mild increased reduction in CTN of ipsilateral parotid; however, in patients with a significant GTV P volume shrinkage, the mean reduction in ipsilateral parotid CTN was greater than the contralateral parotid CTN ($p = 0.07$). Similar reports from Mei Feng et al. [25] and Shouping Xu et al. [26] confirm that the CTN changes are highly patient specific. This forces us to accept the fact that even though all patients received the same dose, the fact that the CTN reduction varied implies that the radiation dose might be just one of the many factors causing the CTN changes.

The tumour and normal structure changes in mean CTN during and after radiation are reported in various studies. Diot et al. [16] observed an increase in CTN of normal lung tissue with an increase in SBRT radiation dose until 35 Gy and thereafter remained unchanged. With subsequent follow-up for 30 months after RT, the rate of CTN increase with dose remained at around 0.24% per gray. Xu et al. [27] 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 –36 HU in lung tumour volumes in patients treated with conventional fractionation dose up to 66.6 grays. De et al. [28] reported that the CTN changes with radiation dose observed in lung tumours were highly patient specific and ranged from 0 to 10 HU/Gy. Howell et al. [18] observed the reduced CTN in post SBRT normal liver after liver irradiation. Thalacker et al. [29] observed the reduction of CTN of white matter by 5 HU after brain irradiation.

Mei Feng et al. [25] reported a decrease in mean CTN of both tumour and parotid glands during the course of radiation in HNC with a fair correlation between CTN reduction and radiation dose for a subset of patients, but also reported that the correlation between volume reductions and CTN reductions in both GTV

and parotid glands were weak. In our study also we observe a positive correlation between the mean CTN reduction and relative volume reduction for GTV P and for GTV N, although the relationship is weak. However, there was no correlation observed between the max CTN reduction and relative volume reduction for GTV N. There was also no correlation observed between the CTN change and the volume change in the both the ipsilateral parotid and contralateral parotid glands.

The patient-specific CTN changes observed in the GTV in this study may be related to the radiation response of the individual patient because 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. [30] reported an increase in blood volume of the primary tumour volume early in the course of RT (after two 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 suggests that an increase in local blood supply, and thereby potentially a source of improved tumour oxygenation, may be an early positive indicator for predicting the therapeutic response at the primary tumour site and disease prognosis of HNC patients. Truong et al. [31] 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 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 tumour cell death as a result of increasing radiation dose causes the tumour to shrink, which contributes to the reduction in tumour CTN.

The mechanism of radiation-induced CTN change in parotid glands is attributed to multiple factors. Heo et al. [32] found that age and obesity are correlated with the size and the CTN change of the major salivary gland. Teshima et al. [33] reported a correlation between decreased saliva production and decreased parotid gland volume in HNC patients receiving radiation. Stephens et al. [34] observed that the damage to the secretory cells and the lack of regenerating the acinar cells with radiation dose contribute to CTN changes in parotid glands. These factors might contribute to the highly complex radiation dose dependence noted in CTN reduction of both the parotid glands [23].

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.

Conclusions

The CTN can be reduced in both the tumour volumes (GTV P and GTV N) and in bilateral parotid glands 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, but no correlation with both the parotid glands. 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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