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FULL PAPER

Radiation-induced CT number changes in GTV and parotid glands during the course of radiation therapy for nasopharyngeal cancer

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Objective: To investigate the changes in CT number (CTN) in gross tumour volume (GTV) and organs at risk (OARs) during the course of radiation therapy (RT) for nasopharyngeal cancer (NPC).

Methods: Daily megavoltage CT (MVCT) data collected from 30 patients with NPC treated with a prescription dose of 70 Gy in 30–33 fractions using helical tomotherapy were retrospectively analyzed. The contours of GTV and OARs on daily MVCTs were obtained by populating the planning contours from planning CT to daily MVCTs with manual editing, if necessary. The changes of GTV and OAR volumes and the histograms of CTN in the GTV and OARs during the course of RT delivery were analyzed.

Results: Volumes of GTV and parotid glands were reduced during the course of radiation treatment, with

an average shrinkage rate of 0.23% per day (range, 0.02–0.8%) and 1.2% per day (range, 0.2–2.3%), respectively. The mean CTN changes in GTV and ipsilateral and contralateral parotid glands were reduced by 52 ± 35 HU, 18 ± 20 HU and 17 ± 22 HU, respectively. For GTV, the CTN and GTV volume decreases were found to be correlated with each other ($p < 0.0001$). No noticeable CTN change was found in the spinal cord and non-specified tissue irradiated with low doses.

Conclusion: The CTN changes in GTV and parotids are measurable during the delivery of fractionated radiotherapy for NPC, were associated with the doses received (the number of fractions delivered) and were patient specific.

Advances in knowledge: The CTN change during radiotherapy is dose dependent and is measurable for NPC.

INTRODUCTION

High-dose gradients from plans with intensity-modulated radiation therapy (IMRT), such as helical tomotherapy, are particularly desirable for head and neck cancer owing to various organs at risk (OARs) adjacent to the target. Image-guided radiotherapy (IGRT) is recommended to ensure the accurate delivery of IMRT. It is widely reported that during radiation therapy (RT) for patients with head and neck cancer, significant anatomical changes can occur during the course of treatment. These changes include tumour regression and overall weight loss.^{1–3} These changes can be detected from images acquired with IGRT and may be accounted for by adaptive radiation therapy (ART),^{2,4–10} where the treatment plan is revised and delivered based on the changing anatomy of the tumour and/or OARs.^{3,5,11–13}

It has been reported that radiation can lead to electron density changes in the lung and liver, as observed from CT

images.^{14–18} The CT number (CTN) changes were found to be associated with radiation injuries.

In RT for head and neck cancer, changes in textural features, such as mean density, were used to characterize structural modifications on parotid glands owing to radiation.¹⁹ In this work, we explored whether radiation could cause CTN changes by examining the daily megavoltage CTs (MVCTs) acquired during IGRT for patients with nasopharyngeal cancer (NPC) and how these changes are associated with the anatomic changes observed for these patients.

METHODS AND MATERIALS

Patient data

Daily MVCT data acquired for 30 patients (24 males and 6 females) with pathologically proven NPCs treated with IGRT using tomotherapy (TomoTherapy®; Accuray Inc.,

Sunnyvale, CA) at the General Hospital of the People's Liberation Army were analyzed. Among these patients, 16 patients were treated with concurrent cisplatin-based chemotherapy during radiotherapy and 14 patients received radiotherapy alone. These patients had Stage I (23.3%), II (43.3%), III (26.7%) and IV (6.7%) NPC, with a median age of 46.5 years, ranging from 10 to 66 years old. For each patient, the gross tumour volume (GTV) (the primary nasopharyngeal tumour) and OARs (e.g. both ipsilateral and contralateral parotid glands and spinal cord) along with other structures were delineated based on the planning CT and MRI registration. The GTV in the planning CT ranged from 10.4 to 100.2 cm³. The prescription dose to GTV was 70 Gy in 30–33 fractions, with treatment duration of 40–45 days. The dose constraint for both parotid glands was $V_{30} \leq 50\%$ (V_{30} is the volume covered by 30 Gy). For every treatment fraction, each patient was immobilized with a thermoplastic mask. A set of MVCT images were acquired in the normal acquisition mode [e.g. jaw width of 4 mm, pitch of 1, 2 or 3 for fine, normal or coarse resolution, with corresponding CT slice thicknesses of 2, 4 or 6 mm (in-plane resolution), respectively], and the patients were then repositioned based on the rigid-body registration of the planning CT and the daily MVCT prior to treatment delivery.

For the data sets selected in this study, the MVCT scanning lengths were sufficient to cover the entire GTV and parotid glands. For the purpose of this analysis, the GTVs were modified to largely exclude air cavity. Effort was made to keep the contouring method consistent in all MVCTs. In addition, a region of non-specified tissue (NST), which is a part of the trapezius muscle a distance away for the slices of the planning target volume and received doses substantially lower than the doses to the parotids and spinal cord, was also delineated from the planning CT. The contours of GTV, OARs (e.g. parotid glands and spinal cord) and NST were obtained on daily MVCTs by populating these contours from planning CTs to the daily CTs via rigid-body registration using a commercial software (Adaptive Plan, TomoTherapy, Accuray) and were edited manually, if necessary. For each patient, the MVCT sets for the first and last fractions and for 1 fraction per week, totalling 7 or 8 sets for patients treated with 30 or 33 fractions, were analyzed.

Data analysis

The selected daily MVCT sets and corresponding contours (e.g. GTV, parotids, spinal cord and NST) were exported in the digital imaging and communications in medicine RT format from the tomotherapy system and analyzed with an in-house software tool developed with MATLAB® v. R2013a (MathWorks, Natick, MA) to determine the volume and CTN in each voxel inside the relevant structures on each daily MVCT set. Histograms of CTN, in Hounsfield unit, for all structures on all selected fractions were obtained and the mean CTN (CTN_{mean}) and mode CTN (CTN_{mode}) values were calculated from each histogram. CTN_{mode} is the CTN at which its probability distribution (e.g. histogram) reaches its maximum. To exclude air, CTNs below –400 HU were omitted from the data analysis of the GTV.

The changes in volume, CTN_{mean} and CTN_{mode} during the course of treatment delivery were analyzed. Two-tailed Pearson's

correlation analysis was carried out to compare the changes in structure volumes and CTNs.

RESULTS

Data from representative cases

From the MVCTs acquired during the course of treatment delivery, detectable changes in CTN were observed for some patients, while significant anatomical changes in volumes were found in most patients. These changes are highly patient specific. Figure 1 shows a representative case with significant changes in the anatomy and CTN during treatment delivery. The shrinkages in GTV and OAR contours between the first (Figure 1a) and last (Figure 1b) fractions are evident. The dose distributions from the first and last fractions overlaid on the MVCT of the last fraction (Figure 1c) indicate that the doses in the ipsilateral and contralateral parotids have increased from the first to the last fraction owing to tumour shrinkage. Figure 1d shows the volume reductions for the parotid glands, 66.2% and 70.1% for the ipsilateral and contralateral glands, respectively, and GTV (25.5%) over the entire treatment course, while the changes in the CTN_{mode} and CTN_{mean} for various structures are presented in Figure 1e,f. It is clear that for this patient, a sizable change in the CTN_{mean} was observed in the GTV, while the changes in other structures are minimal. There was almost no change in the CTN for the NST and spinal cord. The maximum doses to the NST and spinal cord were 20 and 30 Gy, respectively, which are substantially lower than those in the GTV (75 Gy) and parotid glands (65 Gy). This indicates that the observed changes in other structures were not due to the imaging process but were induced by radiation. The CTN histograms for the GTV and parotid glands at different fractions for the same case presented in Figure 1 are shown in Figure 2. Shifts in these histograms, particularly in GTV, were seen as more fractions were delivered. The CTN_{mode} values obtained by fitting with a gaussian for GTV histogram show the same trend as the CTN_{mean} . Figure 3 shows similar data, including changes in the anatomy and CTN for another sample case. It is clear that volumes of the GTV and parotids reduced during the treatment (by 8.3% for the GTV, 40.3% and 43.3% for the ipsilateral and contralateral parotid glands). The CTN_{mean} for GTV decreased as the treatment fraction increased, while it did not change noticeably for all other structures (Figure 3f). The response of CTN for this case is clearly different from that for the case shown in Figure 2. The CTN histograms for the GTV and parotids for this case for the selected fractions are presented in Figure 4. These histograms as well as their CTN_{mode} show a different trend compared with those in Figure 2 for a different case.

CT number and volume changes

Figure 5 presents data for all 30 patients studied including (a) the percentage changes in the volumes of the parotid glands and the GTV during the entire course of treatment, (b) the mean doses of the parotids based on the helical tomotherapy plans and (c) the CTN changes for the GTV and the parotids during the whole treatment course. The volumes of the GTVs and both ipsilateral and contralateral parotid glands were reduced throughout the fractionated RT delivery with reduction rates in ranges of 0.02–0.8%, 0.2–2.3% and 0.7–2.1%, respectively, per treatment fraction. The percentage shrinkage of the ipsilateral

Figure 1. Data for a representative case, changes in the gross tumour volume (GTV) and parotids between the first (a) and last (b) fractions, (c) isodose distributions of the first (solid line) and last (dashed line) fractions overlaid on the megavoltage CT of the last fraction and changes in (d) the volumes of the GTV and parotid glands, (e) the mode of CT number (CTN_{mode}) of the GTV and parotid glands and (f) the mean CT number (CTN) values of the GTV, parotids, non-specified tissue and spinal cord, as functions of delivered radiation dose during the course of radiotherapy. HU, Hounsfield unit.

Figure 2. CT number (CTN) histograms at various fractions for the (a) gross tumour volume, (b) ipsilateral and (c) contralateral parotid glands for the same case as in Figure 1.

parotids (median, $39.3 \pm 15.0\%$) is slightly higher than that of the contralateral parotids (median, $34.2 \pm 13.7\%$). The differences between the mean doses and the volume covered by 30 Gy of the ipsilateral and contralateral parotids based on the plans were statistically significant [30.36 ± 3.27 Gy vs 30.02 ± 3.79 Gy and $37.13 \pm 4.81\%$ vs $36.90 \pm 4.67\%$ (1 standard deviation), $p < 0.0001$]. The differences between the CTN changes in the contralateral and ipsilateral parotids were also significant ($p < 0.001$). Overall, the CTN_{mean} values of all the GTVs were reduced during the whole treatment (Figure 5c). The CTN_{mean} values of the parotid glands were slightly reduced for most of the patients studied. A strong correlation was observed between the relative volume reduction and the CTN_{mean} reduction during

the entire course of treatment for all GTVs studied with a Pearson's correlation coefficient of 0.759 and $p < 0.0001$ (Figure 6). However, there was no correlation ($p = 0.780$) between the relative volume reduction and the CTN_{mode}. In addition, no significant correlation ($p = 0.743$) between the CTN change and the volume change in the parotid glands was seen (Figure 6).

DISCUSSION

It has been well reported that interfraction changes in the tumour and parotid glands during RT for head and neck cancer can be substantial. Barker et al³ demonstrated that nodal and primary tumour volumes assessed on repeated CT of 14 patients

Figure 3. Data for another example case, changes in the gross tumour volume (GTV) and parotids on the daily megavoltage CT between (a) the first and (b) the last fractions, (c) isodose distributions for the first (solid line) and last (dashed line) fractions and changes in (d) the volume and (e) the mode of CT number (CTN_{mode}) of GTV, parotids and (f) mean CT number (CTN) values of the GTV, parotids, spinal cord and non-specific tissue, as functions of the delivered dose. HU, Hounsfield unit.

Figure 4. CT number (CTN) histograms for the sample case as shown in Figure 3 for selected fractions for (a) gross tumour volume, (b) ipsilateral and (c) contralateral parotid glands.

shrunk by about 1.8% per treatment day and that volumes of the parotid glands also decreased by 0.6% per day and shifted medially by up to a few millimetres. Similar findings were shown based on daily MVCT, repeated CT and fludeoxyglucose positron emission tomography.^{1,2,5,11} Hansen et al¹² assessed the

dosimetric impact of interfraction anatomic changes on 13 patients with head and neck cancer treated with IMRT and reported dose increases in OARs. It has been shown that the changes of parotid volumes and positions during RT resulted in an increase of mean doses to the parotid glands by 10%.⁶ This

Figure 5. Volume and CT number (CTN) changes and mean doses for all 30 patients with nasopharyngeal cancer, (a) the percentage changes in the volumes of the parotid glands and the gross tumour volumes (GTVs) during the entire course of the treatment, (b) the mean doses of the ipsilateral parotid (Ipsi_Parotid) and contralateral parotid (Contra_Parotid) from the helical tomotherapy plans and (c) CTN changes for the GTV and the parotid glands during the whole treatment course.

Figure 6. Correlation between the relative volume reduction and the mean CT number (CTN) reduction [in Hounsfield unit (HU)] for gross tumour volumes (GTVs) (a) and parotid glands (b) for all the patients studied.

study shows that the volumes of the GTV, ipsilateral and contralateral parotid glands decreased on an average by 7.4%, 39.3% and 34.3%, respectively, during the whole treatment course (Figure 5). In addition to the dose increases to the parotid glands [the delivered and planned mean dose, 32.77 ± 4.95 Gy vs 30.19 ± 3.51 Gy (1 standard deviation), $p < 0.0001$] similar to previous studies,^{6,11–13} we observed CTN changes in the GTVs and parotid glands and also weight loss on an average by 11%. These changes were increased with the number of fractions delivered, thus, were radiation induced. Similar CTN changes were not observed ($< 3\%$) in the spinal cords and NSTs, where radiation doses were substantially lower than those in the GTVs and parotid glands (20–30 Gy vs 75–65 Gy in maximum doses). The observed CTN change was highly patient specific.

Various ART strategies^{7–9,20–23} have been reported to be effective, to correct for the interfraction dosimetric changes during the RT for head and neck cancer. In particular, the offline adaptation has been shown to be practical.^{9,10,23} However, the optimal timing and/or thresholds to trigger the adaptation and clinical benefit remains to be addressed. The patient-specific CTN change in the GTV observed in this study may be related to the radiation response of individual patients, as the doses to the GTVs were similar (approximately 70 Gy) for all the patients studied. The mechanism behind this CTN change is largely unknown. It has been reported that the pre-treatment tumour blood flow and capillary permeability in patients who achieved locoregional control were significantly higher than in those with treatment failure²⁴ and that low perfusion of head and neck

cancer was associated with higher rates of local failure of RT.²⁵ Tumours that demonstrated CTN reduction may represent regions of improved oxygenation and sensitivity to radiation-induced damages.^{24–26} The mechanisms of underlying radiation-induced CTN change in the parotid glands remain even more unclear. Heo et al²⁷ found that both age and obesity are closely correlated with the size and CTN of the major salivary glands. Factors such as the damage of secretory cells and lack of regeneration of the acinar cells with radiation dose may contribute to the CTN change of parotid glands.^{27–29} The number of cases considered in this exploratory study is too small to truthfully investigate the correlation between CTN changes and local control or treatment-related toxicity data. If the hypothesis that CTN change can measure the radiation response is verified and the mechanism behind is uncovered, then CTN change would potentially be used as an alternative or complementary indicator, to trigger the adaptation in addition to or replacing the dosimetric indicators currently used in ART for head and neck cancer.

A drawback of this study is the use of low soft-tissue contrast in daily MVCTs, which inevitably introduced variations/errors in structure delineation. To reduce the variations, all contours on daily MVCT were generated by first populating the contours from the planning CTs and then manually editing by a single observer, if necessary. Of course, high-dose imaging, deionized and texture-enhanced MVCT would be made possible to improve the soft-tissue contrast.^{30,31} The delineation errors should not significantly affect the observed results, as only the relative and CTN_{mean} change in a structure is of interest here.

In order to verify that the CTN change observed was not contributed by the daily variation of the MVCT imaging, we investigated the stability of the MVCT image quality over a period

of time for the tomotherapy unit used in this study. The MVCTs for the “Cheese” phantom (TomoTherapy, Accuray) and CIRS phantom® Model 062 (CIRS Inc., Norfolk, VA) with a series of plugs of different materials with known electron densities were acquired weekly for a year using the same clinical imaging protocol. The CTNs in these phantom MVCTs were checked. It was noted that there was no noticeable change in CTNs for all densities in the phantoms, implying that there was no variation in MVCT imaging that contributed to the CTN changes observed in the patients with NPC. Similar results were also reported previously.^{32–34}

Very recently, Feng et al³⁵ observed similar CTN changes in patients with various types of head and neck cancers based on diagnostic-quality CTs acquired during the course of RT delivery using an in-room CT (e.g. CT on rails). With diagnostic-quality CT, the delineation uncertainty and CTN measurement error should be small. This study, based on MVCT, confirms that the CTN change can be induced during RT for NPC and is a function of the radiation dose delivered.

CONCLUSION

We observed and quantified CTN changes in the GTV and parotid glands during the fractionated RT for NPC. A decrease by 52 HU in the CTN_{mean} in GTV was detected during the RT course. For the GTVs, CTN changes were found to be correlated with relative volume reductions, while no such correlation was identified in the parotid glands. This radiation-induced CTN change was highly patient specific and thus may be used as an indicator to trigger the ART for head and neck cancer.

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