Original Article

Tumour Shrinkage and Contour Change during Radiotherapy Increase the Dose to Organs at Risk but not the Target Volumes for Head and Neck Cancer Patients Treated on the TomoTherapy HiArt™ System

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Abstract

Aims: To quantify the changes in contours of the target and organs at risk and the differences between planned and delivered doses to the target and organs at risk during the course of radiotherapy in head and neck cancer patients treated with intensity-modulated radiotherapy on the TomoTherapy HiArt™ system.

Materials and methods: Five patients with squamous cell carcinoma of the head and neck treated with radical chemoradiotherapy using the TomoTherapy HiArt system were included in the study. The target volumes were treated to three different dose levels depending on the level of clinical risk for harbouring disease. Patient positions were assessed daily with megavoltage computed tomography (MVCT) and positional correction made before each treatment when necessary. MVCTs were superimposed on to the planning kilovoltage computed tomography images for each patient and target volumes and organ at risk volumes were re-outlined on MVCT images. Doses to clinical target volumes and organs at risk were recalculated to show the actual delivered doses.

Results: There was shrinkage in the volume of the parotid glands during treatment in all cases. The mean volume reduction in the ipsilateral parotid gland was more marked at 30.2%, compared with the contralateral parotid glands. However, the mean percentage dose per fraction increase was higher in the contralateral parotid glands at 24%, compared with the ipsilateral parotids. The calculated doses were higher than the planned doses in all CTV-54, CTV-60 and CTV-68, but the mean dose differences were modest, in the range 1.3–2.4%.

Conclusions: We have shown that there were considerable changes in the volume and dose to the parotids during treatment. The changes in volume and dose to the clinical target volume were more modest in comparison. Adaptive radiotherapy planning can be helpful in improving the dose to the parotid glands. However, its role in the optimisation of the dosage to the clinical target volume is less likely to result in a significant clinical benefit.

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Key words: Head and neck cancer; intensity-modulated radiotherapy; tomotherapy

Introduction

Image-guided radiotherapy (IGRT) and intensity-modulated radiotherapy (IMRT) represent two important technical developments that will probably improve the outcome for appropriately selected patients receiving radiotherapy [1–7]. Several different systems are available for the implementation of IGRT and for the planning and delivery of IMRT. Each system has its own characteristics, which need to be understood and optimised in order to achieve the best performance from the system. Helical tomotherapy provides an elegant integrated solution for the combination of IGRT and IMRT. IMRT is becoming the standard radiotherapy technique used for the treatment of head and neck squamous cell carcinoma [8–10]. IMRT has the capability of providing high dose conformity to complex-shaped target volumes and at the same time sparing critical organs, such as parotid glands, spinal cord, brainstem and mandible. Xerostomia is a significant and common long-term toxicity after radical radiotherapy for head and neck cancer [11]. The dose to the parotid glands typically exceeds 40 Gy with conventional radiotherapy techniques when delivering comprehensive radiation treatment to the head and neck region. IMRT enables significant reductions in the dose to the parotid glands with a reduction in long-term xerostomia when compared with conventional radiation techniques [7,12–14].
Target volume and organ at risk (OAR) delineation is normally carried out on a single set of scans before the course of radiotherapy. Radiotherapy doses are calculated using the same information and radiation treatment plans are not normally amended during the course of treatment. However, the shape and position of target volumes and OARs can change during the course of treatment due to tumour shrinkage and patient weight loss. This can affect the dosimetry of radiation treatment. With the TomoTherapy HiArt™ system, variability in set-up positioning can be minimised by daily megavoltage computed tomography (MVCT) imaging and positional correction. Organ movement is generally not a major issue in radiation treatment of head and neck carcinoma, except for swallowing. Several studies have shown that the dose to the target volume and OARs, especially the parotid glands, can vary significantly due to spatial and volume variability during treatment [15–17], resulting from shrinkage in the tumour and parotid gland volume, and weight loss. Some studies go as far as recommending replanning during the course of IMRT for selected patients in order to ensure adequate doses to target volumes and safe doses to OARs [15,18].

This study aimed to quantify the changes in the volume of the target and OAR structures during the course of radiotherapy in patients treated with IMRT, and to assess whether a replanning strategy needed to be developed. The study assessed the differences between planned and calculated delivered doses to the target and OARs as a result of these changes.

**Materials and Methods**

**Patient Data and Treatment Planning**

Five patients with head and neck cancer treated between January and April 2009 were selected for this retrospective study. All five patients were men, with a median age of 50.8 years (Table 1). They received concurrent chemoradiotherapy, with weekly cisplatin chemotherapy intravenous infusions at 40 mg/m² body surface area and radiotherapy to a dose of 68 Gy in 34 fractions. IMRT was delivered with the TomoTherapy HiArt system.

Table 1

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Primary site</th>
<th>TMN stage</th>
<th>Histology</th>
<th>Concurrent cisplatin</th>
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<td>T1N2aM0</td>
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<td>Yes</td>
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<tr>
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<td>T4N2cM0</td>
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<td>Yes</td>
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<td>3</td>
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<td>52</td>
<td>Supraglottis</td>
<td>T3N2bM0</td>
<td>SCC</td>
<td>Yes</td>
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<tr>
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<td>Tonsil</td>
<td>T1N2aM0</td>
<td>SCC</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>48</td>
<td>Soft palate</td>
<td>T3N2bM0</td>
<td>SCC</td>
<td>Yes</td>
</tr>
</tbody>
</table>

SCC, squamous cell carcinoma.
Assessment of the Change in Geometry and Dose Distribution

Daily MVCT images were acquired before online positional correction, as per our standard IGRT protocol [19]. As daily imaging and positional correction are integral parts of our management, patients were not exposed to additional radiation for the purpose of this study. The clinical imaging protocol requires as short as possible a scan length in order to minimise additional radiation dose. For this project, eight MVCTs were selected for each patient, out of the 34 available. In order to cover the duration of the treatment course, MVCTs from radiotherapy fractions 1, 6, 11, 16, 22, 27, 32 and 34 for each patient were transferred to Prosoma® three-dimensional virtual simulation planning software. These MVCTs were superimposed on to the planning kilovoltage computed tomography images for each patient, and target and OAR volumes were re-outlined on each MVCT image (Fig. 1). The doses were then recalculated from each MVCT to show the actual delivered doses to the CTVs and OARs. The doses were then summated, week by week, to give a total calculated dose. Manual re-outlining of OARs and target volumes was carried out on 40 sets of MVCT scans, eight per patient for the five patients.

One problem in the generation of study data was the result of the limited length of the MVCT imaging, designed to minimise radiation exposure. The imaged volume typically extended from the base of the skull, below the level of the lens, to the mid-cervical spine. As a result, the entire parotid glands were typically not imaged with this technique. In fact, in all five cases the part of the parotid glands superior to the external auditory canals was not included within the MVCT images. Therefore, we carried out a dosimetric analysis based only on the partial volume of the parotid glands that was imaged on each of the MVCTs. We have not provided dos–volume histograms, as these would be unrepresentative. Likewise, the exact clinical significance of dose and volume changes cannot be inferred.

The second problem we encountered was that the GTV of the primary tumour, and to a lesser degree involved lymph nodes, could not be accurately delineated on the MVCT scans. This reflects a limitation of unenhanced computed tomography in general. In practice, accurate delineation of the primary tumour continues to pose a great challenge in radiotherapy in head and neck cancer. All modalities of imaging, including computed tomography, magnetic resonance imaging and FDG positron emission tomography, have limitations in the assessment of true tumour extent [20]. Hence, we concluded that uncertainty in tumour delineation will remain an issue using treatment verification imaging.

The change in the patient contour was evaluated by calculating the volume within the skin outline over the length of the target volume. This method was preferred over simply measuring patient weight loss, as it bore stronger correlation to dosimetric variability within the anatomical region of interest. Patient weight loss may represent a more global change in patient body contour that may not necessarily be within the treatment field. Unfortunately, changes in patient weight were not recorded in a form that could be accessed retrospectively for this study.

**Statistical Analysis**

A simple comparison of volumes was made, within the same patient, to describe the change over time. These changes were also described as percentage changes, compared with

Fig. 1. Megavoltage computed tomography (MVCT) images with target volumes and organs at risk outlined. Left: MVCT image at fraction 1. Right: MVCT image at fraction 34. Slight pitch is evident in the positioning, which cannot be corrected by image-guided radiotherapy. Note that the parotid glands have a higher density after treatment.
the original volumes at the time of planning. A similar comparison was made for the dose and dose per fraction changes over time. Linear regression was used to compare the parotid gland volume reduction against the dose, both planned and calculated, using a Microsoft Excel spreadsheet.

Results

We were able to carry out a dosimetric analysis on all five cases for the contralateral parotid glands, but only four cases for the ipsilateral parotid glands. In case 2 it was not outlined at the outset, as it lay within a CTV-60. The CTVs outlined in these cases included four CTV-54 volumes, nine CTV-60 volumes and eight CTV-68 volumes. No attempt was made to summate CTVs of the same dose level in each case so that the interference to the dose-volume histogram data could be kept to a minimum.

The most striking feature was a substantial shrinkage in the volume of both the parotid glands during treatment, in all cases. The mean volume reduction in the contralateral parotid gland was 17.5%, with a range of 15.6–48.5%. Figure 2a shows the percentage volume reduction in the contralateral parotid glands in five cases over the course of the radiotherapy. Figure 2b shows the percentage dose per fraction increase in the contralateral parotid glands. The mean planned dose to the contralateral parotid gland for the five cases was 26.2 Gy (range 23.8–28.6 Gy), and this increased by a mean of 7.3 Gy (range 1.1–11.6 Gy), in the part of the gland that was assessable (Table 2). The dose per fraction to the contralateral parotid gland therefore increased in all five cases throughout the course of radiotherapy treatment, by a mean of 19.3% (range 8.2–41.5%).

The volume changes in the ipsilateral parotid glands were more marked than the volume changes in the contralateral glands, with a mean volume reduction of 30.2% and a range of 17.1–55.8%, consistent with them having received higher planned doses. Figure 3a shows the percentage volume change and Fig. 3b the percentage dose increase per fraction in the ipsilateral parotid glands for cases 1, 3, 4 and 5. Case 2 ipsilateral parotid gland data are not included as it was not outlined in the original treatment plan. The mean planned dose to the ipsilateral parotid glands was 33.8 Gy (range from 26.8–43.2 Gy) (Table 3), in the part of the gland that could be assessed. The mean percentage dose per fraction increase in the ipsilateral parotid gland was noted to be less marked compared with the contralateral parotid gland at 8.9% (range 7.22–11.32%). The mean difference between planned and calculated doses was 7.6 Gy (range 2.5–19 Gy) (Table 3).

The volume reduction in both contralateral and ipsilateral parotid gland volumes was most marked for case 5, compared with the other cases. Although the planned dose (i.e. 43.2 Gy) and the calculated dose (i.e. 62.2 Gy) to the ipsilateral parotid gland were the highest of all the cases, this was not so for the contralateral gland (23.8 and 35.4 Gy, respectively) (Tables 2 and 3). The observed volume change in the parotid glands in case 5 cannot be fully explained on the basis of the total dose or the dose per fraction. Whether this might have biological significance, such as higher sensitivity, is not known.

Considering the contralateral and ipsilateral parotid glands together, there was no significant relationship between the percentage volume reduction and the planned dose (R = 0.50, R² = 0.25, P = 0.17). Although the same comparison using the recalculated dose did show a weak relationship (R = 0.74, R² = 0.54, P = 0.02), this was the result of a single high dose point, without which no correlation would be seen. Although parotid shrinkage probably has some relationship with dose, the details could not be established from this small series.

There was no change to the spinal cord volume as expected. The mean dose difference between the planned and calculated Dmax was also small at 0.2 Gy (0.5%).

With the exception of case 2, all cases had one CTV-54 volume outlined. The mean volume change in CTV-54 throughout radiotherapy was 10.7% (5.5–18.4%), as a result of patient shrinkage. The calculated doses were higher than the planned doses in all CTV-54, but the mean dose difference was only 1.1 Gy (1.9%) (Fig. 4).

The CTV-60 volume encompassed the intermediate-risk target volume, which was treated to a dose of 60 Gy in 34 fractions. In total, nine separate CTV-60 volumes were outlined in the five patients. The mean reduction in the CTV-60 volume over the treatment course was 7.1% (range 0–22%). In all cases, the calculated dose to CTV-60 was slightly higher than the planned dose, with a mean dose difference of 1.5 Gy (2.4%) (Fig. 5).
The CTV-68 volumes encompassed the high-risk target, which was treated to a dose of 68 Gy in 34 fractions. The mean volume change was 5.8% for the CTV-68 volume. This mean volume change is noted to be less than that for CTV-54 and CTV-60. Once again, we observed that the calculated doses for all CTV-68 were higher than the planned doses. However, the mean dose difference was rather small at 0.9 Gy (1.3%) (Fig. 6).

The change in the patient contour was evaluated by calculating the volume within the skin outline over the length of the target volume. A reduction in volumes was observed in all cases. The mean reduction in volume was 350 ml (range 289–428 ml).

**Table 2**

<table>
<thead>
<tr>
<th>Case</th>
<th>Planned dose (Gy)</th>
<th>Calculated dose (Gy)</th>
<th>Dose difference (Gy)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>24.1</td>
<td>25.5</td>
<td>1.4</td>
</tr>
<tr>
<td>2</td>
<td>27.0</td>
<td>38.6</td>
<td>11.6</td>
</tr>
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<td>27.3</td>
<td>38.1</td>
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</tr>
<tr>
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<td>23.8</td>
<td>35.4</td>
<td>11.5</td>
</tr>
<tr>
<td>Overall mean dose</td>
<td>26.2</td>
<td>33.5</td>
<td>7.3</td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Case</th>
<th>Planned dose (Gy)</th>
<th>Calculated dose (Gy)</th>
<th>Dose difference (Gy)</th>
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<td>26.8</td>
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<tr>
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<td>35.8</td>
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<tr>
<td>4</td>
<td>43.2</td>
<td>62.2</td>
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<tr>
<td>Overall mean dose</td>
<td>33.7</td>
<td>38.5</td>
<td>7.6</td>
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**Discussion**

That excellent dose distributions can be achieved with IMRT, using tomotherapy or other hardware and software solutions, is well described [21–24]. This particularly applies to the treatment of complex target volumes, including those with a concave shape [25].

Existing evidence for the clinical value of IMRT is now compelling [6]. Although there is only modest randomised trial evidence of the superiority of IMRT over conventional conformal radiotherapy, some studies have been published, and others are eagerly awaited. Randomised studies have shown an advantage in terms of reduced toxicity for patients treated with IMRT for head and neck cancer and also breast cancer [2,5], and full results from further randomised trials in both areas are pending [7,26]. The major body of evidence supporting the use of IMRT is in the form of cohort studies. These clearly show an advantage of reduced toxicity in patients with head and neck cancer [27,28], as well as other tumour types [29–31].

One concern with IMRT, where the high dose region is highly conformed to the planning target volumes, is that any changes in target volume and geometry during treatment might pose a risk for target geographical miss or under-dosage. An additional issue is that OARs have been observed to have received higher than the planned doses due to weight loss and tumour shrinkage. Vásquez Osorio et al. [32] used a non-rigid registration method to assess the local anatomical changes in the parotid glands and submandibular glands in 10 oropharyngeal cancer patients. They reported a significant volume loss in both spared parotid glands (5 ± 4%) and submandibular glands
(11 ± 7%), with an associated change in the mean dose to the glands. They observed a medial shift in the lateral part of the irradiated parotid gland by an average of 3 mm, whereas the irradiated submandibular gland shifted cranially. Robar et al. [33] assessed the spatial and dosimetry changes in OAR using repeated weekly verification computed tomography. They reported similar volume and spatial changes in the parotid glands [33]. In our study, we observed a significant reduction in volumes for both the contralateral and ipsilateral parotid glands. The ipsilateral parotid gland volume reduction was larger than the change in the contralateral parotid gland in each patient, although the doses were generally higher. However, there was no definite correlation between volume shrinkage and dose, either planned or recalculated, in this small series. Although not quantified in this study, we observed a medial shift of parotid glands into adjacent CTVs through the course of radiotherapy due to the change in patient contour. This resulted in a gradual increase in the dose per fraction to the parotid gland over the course of treatment.

In the study by Barker et al. [16], changes in the tumour volume during radiotherapy were studied in 14 patients using an in-room kilovoltage computed tomography scanner in the treatment position. They observed a GTV volume reduction at a median rate of 0.2 cm³ per treatment day (1.8% of the initial volume per treatment day). However, the dosimetric effect of volumetric and geometric changes was not assessed in their study.

Hansen et al. [15] reported a retrospective study of 13 patients treated for locally advanced head and neck cancer with IMRT concurrent with platinum-based chemotherapy. Patients had a second computed tomography scan mid-way through radiotherapy prompted by a clinically observed change in patient anatomy and/or weight loss. The second computed tomography scans were used to generate a second IMRT plan, which was used to complete the remaining course of radiation treatment. To take into account the volumetric and geometric changes, hybrid IMRT plans were generated by applying the beam configuration of the first IMRT plan to the second computed tomography scan to assess dosimetric changes. When replanning and non-replanning were compared, a reduced dose to target volumes and an increased dose to OARs were observed. The dose to 95% of the planning target volume or the GTV and CTV were reported to have reduced by 0.8–6.3 Gy and 0.2–7.4 Gy, in 92% of studied patients. The $D_{\text{max}}$ was increased by 0.2–15.4 Gy to the spinal cord and 0.6–8.1 Gy to the brainstem. Unlike Hansen et al. [15], the observed increase in mean $D_{\text{max}}$ to the spinal cord in our series was very small indeed at 0.2 Gy.

Wu et al. [18] reported a retrospective study on the use of adaptive replanning strategies to account for tumour anatomical and volumetric change in head and neck IMRT. Different replanning strategies were investigated with different margins of 1, 3 and 5 mm. They assessed single mid-course replanning, alternative week replanning and weekly replanning strategies. The parotid gland mean dose was observed to have increased by an average of 10%. They concluded that shrinkage does not result in significant dosimetric differences in target and critical structures, with the exception of the parotid glands. This is entirely consistent with our results.

In our experience, it was not possible to accurately measure the shrinkage in tumour volume during the course of treatment using the unenhanced MVCT images. However, a reduction in CTV was observed due to the change in body contour within the treatment volume. The CTV-54 volume reduction was more marked than the volume reduction observed in CTV-60 and CTV-68. In all cases, the calculated delivered dose to the CTVs of all three dose levels revealed a higher than planned dose. The largest dose difference was noted in CTV-60, although the dose difference of 2.4% was very modest.

With studies highlighting measurable changes in geometry occurring throughout the course of radiotherapy treatment and its potential dosimetric consequences, the role of adaptive radiotherapy treatment was examined as a strategy to overcome this pitfall. The development of adaptive radiotherapy strategy would take into account these treatment-related geometric and volumetric changes. The potential benefit of adaptive radiotherapy in our series would be twofold. One advantage is the potential of a reduction in dose to the parotid gland. The other is the potential improvement in dose to the target volumes. From our series, we observed no
under-dosage of CTVs across all three dose levels in all cases. The mean dose increase to CTV-54, CTV-60 and CTV-68 was very modest indeed (1.1, 1.5 and 0.9 Gy, respectively). Hence, we concluded that replanning during the course of radiation treatment to optimise the dose to the CTV is probably not necessary. However, there may be a significant benefit with adaptive strategy in improving the dose to the parotid glands.

Acknowledgements

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References


