Thickness difference of parotid glands during IMRT and association with radiation dose

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Abstract

Purpose: Measuring parotid thickness changes in patients treated with IMRT for head–neck tumor (HNC) and surveying connection with treatment-related parameters.

Patients and materials: Data of 84 patients treated with IMRT for various HNC were pooled from three organizations. Parotid disfigurement and normal Hounsfield number changes (DHU) were assessed through MVCT (with Helical Tomotherapy) or demonstrative kVCT pictures taken at the treatment begin/end. Parotids were outlined in the main picture and proliferated to the last utilizing a formerly approved calculation in light of flexible enlistment. The connection amongst's DHU and a few treatment-related parameters was tried; at that point, strategic uni-and multi-variate examinations taking “extensive” DHU as end-call attention to did. Because of the better picture quality, investigations were rehashed considering just kVCT information. Results: DHU was negative in 116/168 parotids (69%; for kVCT patients: 72/92, 78%). The normal DHU was fundamentally not the same as zero (7.3, 0.20–0.25 HU/part, p < 0.001). Individual DHU was profoundly associated with parotid misshapening both regarding volume change and mean estimation of the Jacobian of the twisting field (Jac_mean), and with neck thickness variety; these connections were much stronger for kVCT information. Calculated examinations considering DHU < 11 (quartile esteem) as the end-point demonstrated a two-variable model including vast misshapening (Jac_mean < 0.68) and introductory neck thickness to be the most prescient factors (p < 0.0005, AUC = 0.683; AUC = 0.776 for kVCT); the odd proportion of extensive versus mod-erate/little parotid twisting was 3.8 and 8.0 for the entire and the kVCT populace separately.

Conclusions: Parotid thickness diminished in many patients amid IMRT and this wonder was profoundly corresponded with parotid twisting. The individual appraisal of thickness changes was profoundly solid just with indicative KvCT. Thickness changes ought to be considered as an extra target estimation of early parotid radiation-initiated alterations; additionally inquire about is justified.

The increasing availability of imaging before, during and after Radiotherapy can be well considered as a huge bank of biological information: early reactions during and immediately after the treatment can induce changes in the imaging characteristics of the irradiated tissues. These changes can be associated to different early reactions and can be followed (or not) by late appearance of visible signs of the irradiation that can further be correlated (or not) with the insurgence of late and chronic, clinically measurable, symptoms [1]. In this scenario, early reactions of irradiated tissues may be scored by the assessment of image-related parameters: in particular, quantitative, objectively measurable, scores should be preferred.

When considering computed tomography (CT), several parameters may be considered such as volume variation, organ deformation or density variation [2–4]. Importantly, the large spread of in-room CT imaging is hugely contributing in increasing this field, although most in-room CT techniques are still sub-optimal com-pared to high-contrast/high-resolution CT; several authors recently reported interesting results when considering cone-beam CT (kV or MV) or MV helical CT in Tomotherapy frequently taken (i.e. daily/weekly) during treatment [5–7].

When considering the early effects during radiotherapy of head–neck cancer, parotids are known to significantly shrink and this event has been reported to be correlated with a number of pre-treatment clinical and dosimetric parameters, as well as weight loss/patient thickness reduction [7]. Although not fully rec-ognized, several investigations suggested that parotid deformation may be related to complex structural and functional modifications.
of the glands with high potential in the field of prediction and modeling of xerostomia [7–13]. The need to measure the mind boggling disfigurements happening amid Radiotherapy, pushed us to create techniques in view of the use of flexible enrollment; in particular, the guide of the purported Jacobian (Jac) of the change connected to the first picture is extremely encouraging in speaking to a natural, moderately simple apparatus to portray parotid twisting [11]. Jac speaks to the guide of the level of extension/compres-sion of the voxels of a specific structure and has been connected in the radiotherapy setting in couple of circumstances [11,14,15]. Thickness is naturally estimated by CT and after that can be likewise considered as a conceivably vital score depicting how the parotid struc-ture/ware is changed amid treatment; notwithstanding, up to now the estimation of this parameter is missing [16,17]. The likelihood to relate twisting with thickness variety could likewise be critical, being both the glandular volume variety and the rel-a-tive weight of the fat segment liable to be corresponded with the glandular discharge limit [12,13,18,19].

Within a project dealing with the impact of organ deformation during head–neck Intensity-Modulated Radiotherapy (IMRT), den-sity changes measured with MVCT or kVCT of a large number of pa-tients were investigated.

Materials and methods

Patients and treatment characteristics

Data of 168 parotid glands of 84 patients from three Institutions treated for different Head and neck cancer were pooled. Median patient’s age was 59 years (range: 29–86 years). Most patients (79/84, 94%) didn’t undergo upfront surgery. 76/84 (90.5%) pa-tients received chemotherapy (before Radiotherapy: 18; concomi-tant: 70; both: 12).

Elective node chains were contoured and defined as CTV2, while the tumor volume + involved nodes (or tumor bed in case of adjuvant intent) were contoured as CTV1. In all Institutions, for all considered CTVs an isotropic expansion of 5 mm was applied for PTV definition.

Sixty-six patients (78.6%) were treated with a simultaneous integrated boost approach (SIB), delivering 48.6–58.1 Gy (1.66–1.8 Gy/day) on elective node chains (PTV2) and 55.4–70 Gy (1.95–2.2 Gy/day) on tumor or tumor bed (PTV1). The other pa-tients were treated with a sequential approach delivering 50.4–67.6 Gy (1.2–2.25 Gy/day) on PTV2 and 50.4–78 Gy (1.2–2.33 Gy/day) on PTV1.

All patients were treated with IMRT: 38 patients (from one Institution) with the Helical Tomotherapy Unit (Hi-Art II), 46 (from two Institutions) with Linac-IMRT, in dynamic or step-shoot modality.

In all Institutes, an inverse planning optimization approach was followed with the goal to deliver P95% of the prescribed dose to P95% of PTV volumes, while keeping the dose as homogeneous as possible and sparing both contro- and omo-lateral parotid glands without compromising PTVs coverage. Different dose–vol-u-me constraints and optimization approaches were applied in the different institutions, generating a wide range of parotid DVH shapes.

Imaging procedures

Parotid deformation was evaluated through images taken at the start and at the end of the treatment. More specifically, in one institute MVCT taken with the Helical Tomotherapy Unit on the first and last day of the treatment were considered (image matrix of 512 512 pixels, pixel size of 0.754 0.754 mm², slice thick-ness of 4 or 6 mm). In the other two centers, diagnostic images were acquired with multi-slice Helical CT (KVCT) scanners. KVCT images were taken at the first fraction and during the last week of the treatment, using similar protocols (image matrices of 512 512 pixels, voxel sizes of 0.977 0.977 2.5 mm³ or 1.172 1.172 3 mm³; acquisition parameters: 120 kV; 200 mAs in one Institute, 300 mAs in the other).

These KVCTs images were performed as part of a pilot study with the aim of identifying those patients that could take advan-tage from adaptive re-planing.

Image registration and contour propagation

In order to obtain a spatial correspondence of the parotid glands in image studies acquired in different times, KVCT or MVCT acquired at the first fraction were registered to KVCT (or MVCT) acquired at the end of the treatment, using a non-rigid approach based on free-form deformation (FFD) and B-splines [20]. The reg-istration method consisted of a preliminary stage of rigid motion recovery; after that, local deformable transformation was esti-mated using mutual information, as similarity measure, and a mul-ti-resolution strategy for the image grid and deformation grid refinement, as proposed by Mattes et al.[21].

Manual contours of the parotid glands, delineated on the images of the first fraction by experts, were then automatically propagated to the images at the end of treatment using a dedicated algorithm [20]: these new contours well fitted the modified shape of parotid glands induced by Radiotherapy, with the advantage of avoiding a subjective and time-consuming re-contouring (Fig. 1). The contouring of parotids on MVCT are known to be affected by a higher uncertainty; however, image quality was found to be suf-ficient for describing parotid shrinkage as better discussed in [7,11]; moreover, our contour propagation algorithm was previ-ously found to be sufficiently accurate, being comparable to in-ter-observer uncertainty in delineating parotids on the last fraction MVCT [20]. A visual verification of the adequacy of the propagated contour with respect to the parotid anatomical shape was carried out by a human observer, in all MVCT and KVCT image studies.

Quantitative assessment of parotid spatial deformation and density variation

The substance of disfigurement of each voxel having a place with the parotid organs volume, as distinguished by the manual forms, was evaluated by the Jacobian of the misshapen field computed by picture regis-tration [11]. The Jacobian quantitatively evaluated the shrinkage or extension of the minute volume component, fixated on each picture voxel: Jac = 1 distinguishes voxels whose volume does not change, Jac > 1 growing voxels and Jac < 1 contracting voxels.

The normal estimation of Jacobian inside the organ (Jac_mean) might be surveyed as a quantitative, engineered score of distortion; in addition, the Jacobian-volume-histogram (JVs) was likewise previ-ously presented: it dided out to each container the volume portion an incentive with a pressure or extension bigger than that demonstrated by the receptacle itself, along these lines coming about reasonably and formally comparable to a traditional DVH [11].

The estimation of thickness estimations of parotid organs in kVCT pictures can be influenced by metal antiques because of dental filling: to beat this issue, a strategy for standardized metal ancient rarity lessening (NMAR) was connected [22]; this technique depends on clas-sical sinogram inpainting strategies that utilization insertion to com-plete the sinogram, where metal-influenced values are dealt with as missing information; the interjection method is upgraded to save edge data. Information detailed in the writing on ghost stud-ies demonstrate that metal relics lessening techniques in light of sinogram inpainting can reestablish picture quality, by giving reestablished
average HU values closer to the real HU values and acting in reducing standard deviation [23]. The evaluation of thickness variation was performed by estimating the mean force esteem (Hounsfield units, HU) and standard deviation inside the entire parotid volume outlined by the manual and proliferated shapes on both the main part and the finish of treatment pictures. Thickness variations were measured as far as normal HU change amongst last and first part (DHU); because of the direct connection amongst HU and thickness in the generally little scope of variety of this investigation, DHU estimates taken with both kVCT and MVCT might be utilized for the reason. For kVCT patients, being a half-treatment CT accessible for all patients, thickness varieties at half treatment were additionally surveyed, with the plan to assess the connection between’s thickness changes at half treatment and at end-treatment.

Analyses

The difference from zero was tested in the whole population and separately in the MVCT and kVCT subgroups (t-test).

The correlation between DHU and a number of parameters was tested by the Spearman test. The considered variables were: che-motherapy, previous surgery, type of cancer (nasopharynx vs other), PTVs volume, age, prescribed dose, daily dose, initial parotid volume, mean parotid dose, fraction of parotid receiving more than 10, 15, 20, 30, 40 Gy (V10–V40), % parotid volume variation, neck half-thickness variation (measured at C2, in the normal neck direc-tion in case of lateral tumor, Ds), weight variation, mean Jac (Jac_mean), % fraction of voxels with Jac < 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3 (Jac0.9–Jac0.3).

Analyses were repeated when only considering kVCT data, due to the reduced noise concerning density estimate within parotids.

A logistic univariate analysis was performed considering the DHU larger than the quartile value (11 HU) as end-point, identi-fying the largely changing parotids. Best cut-off values of the most predictive continuous variables were assessed by ROC analysis. Stepwise multi-variate analyses were performed taking the most predictive factors (p < 0.10) at univariate analysis. The predictive value of the models was assessed by the area under the ROC curve (AUC). The analyses were repeated for the whole and the kVCT population.

The correlation between half-therapy and end-therapy density changes was assessed by the Spearman test (kVCT patients).

Results

Density variation

A summary of DHU data in the whole population and in the two MVCT/kVCT subgroups is reported in Table 1.

DHU was <0 in 116/168 parotids (69%); this fraction was larger for kVCT (72/92, 78%). On average, the mean DHU was 7.3 (9.3 for MVCT vs 5.6 for kVCT, p = 0.17), corresponding to about 0.20–0.25 HU/fraction. The SD of the distribution of DHU is much higher for MVCT than for kVCT patients (24.3 vs 7.4) due to the higher noise of MVCT compared to diagnostic kVCT images; the difference from zero of the average DHU is significant also for MVCT patients (p = 0.02 vs 0.0001 for kVCT patients).

Concerning kVCT patients, the average DHU at half therapy was 4.4 (1SD=6.5); DHU at half-therapy was highly correlated with DHU at end-therapy (R = 0.62, p < 0.0001). This result also shows that most of density changes occurs in the first part of the treatment.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>All parotids</th>
<th>MVCT</th>
<th>kVCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean DHU</td>
<td>7.3</td>
<td>9.3</td>
<td>5.6</td>
</tr>
<tr>
<td>Median DHU</td>
<td>4.6</td>
<td>1.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Standard Deviation DHU</td>
<td>17.1</td>
<td>24.3</td>
<td>7.4</td>
</tr>
<tr>
<td>Max DHU</td>
<td>+24.0</td>
<td>+24.0</td>
<td>+13.8</td>
</tr>
<tr>
<td>Min DHU</td>
<td>94</td>
<td>94</td>
<td>27.9</td>
</tr>
<tr>
<td>Lower quartile</td>
<td>11.0</td>
<td>12.7</td>
<td>10.5</td>
</tr>
<tr>
<td>Higher quartile</td>
<td>+1.9</td>
<td>+4.5</td>
<td>1.0</td>
</tr>
<tr>
<td>NL with DHU &lt; 0</td>
<td>116</td>
<td>44</td>
<td>72</td>
</tr>
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</table>

Analyses were repeated when only considering kVCT data, due to the reduced noise concerning density estimate within parotids.

A summary of the results concerning the correlation tests is re-port ed in Table 2 (variables with p-value < 0.20). When considering the whole population, the pre-treatment variables mostly corre-lated with DHU were PTV volume (p = 0.015), % overlap between PTV and parotid (p = 0.02), initial parotid volume (p = 0.048) and secondarily initial neck thickness (p = 0.10), V40 (p = 0.13) and age (p = 0.11); in particular larger PTV volumes, larger parotids, lar-ger neck thickness and younger age predict a larger decrease of DHU. When considering the kVCT group, better correlations were found for initial neck thickness (p = 0.03) and age (p = 0.13).

Correlation between density variation and pre-treatment factors

As can be appreciated, DHU well correlates with most Jac parameters, being Jac_mean the most predictive one (p = 0.004, R = 0.22); parotid volume reduction and thickness variation were also highly correlated, absolute thickness variation being the most predictive (p = 0.0005, R = 0.27).

In Fig. 2, the plot of DHU against parotid volume variation is shown. When considering kVCT patients, the Jac parameters (Jac_mean best predictor) and thickness variations were much...
thickness reduction, parotid volume reduction and JVH-based populations: summary of the results are reported in Table 3 and Fig. 3.

Modeling large density variations

p = 0.0005; volume variation: R = 0.23, p = 0.029).

Summary of correlation tests (Spearman test, p ≤ 0.20): DHU vs pre-treatment-related parameters for all parotids and kVCT parotids.

Table 2

<table>
<thead>
<tr>
<th>Parameters</th>
<th>All parotids (n = 168)</th>
<th>kVCT (n = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>p-Value</td>
</tr>
<tr>
<td>Age</td>
<td>0.12</td>
<td>0.13</td>
</tr>
<tr>
<td>PTV volume</td>
<td>0.19</td>
<td>0.015</td>
</tr>
<tr>
<td>% Overlap PTV-parotid</td>
<td>0.18</td>
<td>0.02</td>
</tr>
<tr>
<td>Initial parotid volume</td>
<td>0.15</td>
<td>0.05</td>
</tr>
<tr>
<td>Initial neck thickness</td>
<td>0.13</td>
<td>0.10</td>
</tr>
<tr>
<td>V30</td>
<td>0.11</td>
<td>0.19</td>
</tr>
<tr>
<td>V40</td>
<td>0.12</td>
<td>0.13</td>
</tr>
<tr>
<td>DVolume&lt;cc</td>
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<td>0.004</td>
</tr>
<tr>
<td>DVolume%</td>
<td>0.23</td>
<td>0.003</td>
</tr>
<tr>
<td>D&lt; cm</td>
<td>0.27</td>
<td>0.0005</td>
</tr>
<tr>
<td>D&lt; %</td>
<td>0.25</td>
<td>0.001</td>
</tr>
<tr>
<td>Jac_mean</td>
<td>0.22</td>
<td>0.004</td>
</tr>
<tr>
<td>Jac0.2</td>
<td>0.21</td>
<td>0.008</td>
</tr>
<tr>
<td>Jac0.3</td>
<td>0.20</td>
<td>0.01</td>
</tr>
<tr>
<td>Jac0.4</td>
<td>0.18</td>
<td>0.02</td>
</tr>
<tr>
<td>Jac0.5</td>
<td>0.17</td>
<td>0.03</td>
</tr>
<tr>
<td>Jac0.6</td>
<td>0.20</td>
<td>0.01</td>
</tr>
<tr>
<td>Jac0.7</td>
<td>0.20</td>
<td>0.01</td>
</tr>
<tr>
<td>Jac0.8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Jac0.9</td>
<td>0.16</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Discussion and conclusions

In actuality, no noteworthy varieties were found in the ROI for kVCT pictures, neither connection with thickness changes in the parotids.

One of the significant aftereffects of our examination is the solid relationship be-tween parotid disfigurement and thickness lessening. Specifically, jacobian-based parameters, communicating the guide of the voxel-by-voxel pressure inside the organs, were observed to be exceptionally pre-dictive of thickness decrease. Additionally, the parotid volume lessening and the neck thickness decrease were observed to be corresponded with thickness changes, in spite of the fact that with the probability of utilizing quantitative data from pictures taken amid (and after) Radiotherapy is a developing field of inves-tigation in present day radiotherapy, broadly utilizing IGRT and imple-menting versatile techniques. Picture based scoring of lethality may offer target instruments for “estimating” the radiation-in-duced harm [1,5] with substantial potential in foreseeing singular responses and perhaps in adjusting the treatment, essentially to re-duce poisonous quality.

The paradigmatic situation of parotid morphological and func-tional changes estimated by imaging strategies is extremely charming; the to a great extent obvious impact of parotid shrinkage could be utilized as a surrogate of radiation-actuated early responses [7–13]. The reasonable relationship between’s parotid misshapening and various clini-cal/anatomical/dosimetric parameters is extremely encouraging [8,11]. Inside this photo, the option of the basic estimation of parotid thickness could be an essential, extra measure of a probable surrogate of utilitarian changes. Parotid thickness has been re-portcd to be related with age [18,24] and thusly to the estimation of the fibro-greasy part that is relied upon to be corresponded to the diminishment of the organ usefulness.

Thickness changes because of radiotherapy may likewise be because of more unpredictable instruments, including incendiary responses; be that as it may, the predominance of a critical decrease of thickness has been re-portcd in few investigations [16,17]: as of late, preparatory outcomes on 16 patients treated with picture guided IMRT for various head-neck tumors were ac-counted for, demonstrating a normal lessening of parotid thickness around 0.30 HU/part [17] which well com-pares with our discoveries (0.20–0.25 HU/division).

Our work is the main huge multi-focus examine unmistakably announcing this wonder in a substantial partner of patients, more apparent while considering symptomatic kVCT.

The higher clamor of in-room imaging (like MVCTs) is a notable issue that restricts the unwavering quality of thickness estimations in this circumstance where a moderately little impact is normal. At that point, despite the fact that the pervasive impact of parotid thickness lessening was vis-ible and measurably huge in our MVCT populace, the indi-vidual appraisal of little thickness varieties in parotids through MVCT is exceedingly indeterminate. MVCTs pictures could be perhaps utilized for singular thickness changes by re-normalizing HU esteem
following the strategy here utilized (utilizing the HU change in a ROI outside the lighted volume); investigating this probability is outside the points of current examination.

The reason of this impact might be theorized as due to a preva-loaned impact of loss of number and measurement of acinar cells, with a subsequent relative increment of the greasy segment of the organ prompting the normal thickness decrease; obviously, this speculation needs more affirmation.

Strikingly, a few specialists proposed that the lessening of salivary stream is related with this wonder, so that, the estimation of thickness changes is contender to end up an addi-tional simple to-gauge and hearty useful score [12,18,19,26].
Curiously, a few specialists proposed that the diminishment of salivary stream would decrease; obviously, this theory needs more affirmation.

The combination of morphological and density information measured with other imaging modalities (in particular, diffusion MRI) gives high promise to better quantify and model functional changes within the parotids [9,10,27–32].

Strangely, the best calculated model while considering kVCT information incorporates Jac_mean and the underlying half-thickness of the neck, recommending that bigger patients tend to demonstrate a bigger abatement in thickness; in any case, this outcome is significantly less vigorous than the effect of misshapening and ought to be affirmed in a bigger populace. In addition, neck thickness was discovered related with age and weight variety in our populace, so the way that neck thick-ness could be a surrogate of these factors (essentially age) ought not be prohibited.

Volume variety and in addition Jacobian-based distortion param-eters have as of late been appeared to be connected with dose–volume parameters [7,8,11].

Here, DVH parameters were feebly connected with thickness changes while thickness changes were profundely associated with parotid misshapening; this finding in a roundabout way proposes that both parotid twisting and thickness changes might be just somewhat clarified by the arranged measurements dissemination; then again, the solid relationship between’s parotid shrinkage and thickness decrease im-handles that early distortion/volume misfortune might be useful in survey ing the most early-responding patients. As of late, an unmistakable relationship between’s initial parotid shrinkage and thickness decrease im-handles that early

In actuality, no noteworthy varieties were found in the ROI for kVCT pictures, neither relationship with thickness changes in the parotids.

One of the significant aftereffects of our investigation is the solid connection be-tween parotid distortion and thickness decrease. Specifically, jacobian-based parameters, communicating the guide of the voxel-by-voxel pressure inside the organs, were observed to be exceedingly pre-dictive of thickness diminishment. Essentially, the parotid volume decrease and the neck thickness diminishment were observed to be connected with thickness changes, in spite of the fact that with a littler prescient esteem.

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Curiously, a few specialists proposed that the diminishment of salivary stream is related with this marvel, so that, the estimation of thickness changes is possibility to wind up an ad-tional simple to-quantify and vigorous useful score [12,18,19,26].

The combination of morphological and density information with direct functional information measured with other imaging
Indeed, even the likelihood to identify thickness changes in the early period of the treatment and their relationship with the progressions toward the finish of the treatment should be examined. On a basic level, the wonder could be too little to be heartily recognized in the early period of the treatment because of picture clamor and intra-scanner varieties. Around this point, it is by all accounts clear that MVCT pictures can't be utilized for this point, as already dis-cussed; concerning symptomatic kVCT, the preparatory outcomes here detailed demonstrate an exceptionally solid connection between's thickness changes amid the primary portion of the treatment and at end-treatment. Additionally, it appears that the majority of the thickness variety happen amid the main portion of the treatment.

In spite of preparatory, this outcome is promising in recommending a clinically doable application in distinguishing early responding patients.

In the thought about scope of HU, both thickness and electron sanctum sity varieties are direct with HU. A change around 15 HU is pretty much comparing to an adjustment in thickness of around 0.01 g/cm3, which may considered "pertinent" in the parotid setting if consid-ering that the contrast between fat tissue and water is around 70– 80 HU (around 0.05 g/cm3) [33].

The significance of the fact of the matter is obvious, as an early recognition of expansive thickness changes could have the capability of doing method of reasoning picture scoring based versatile techniques [27,34,35].

Regardless, we have to find out about the fleeting (and most likely spatial) example of the thickness changes amid the treatment keeping in mind the end goal to apply these ideas. An examination on this point is very advance.
References


