Adaptation Radiotherapy of Head and Neck Cancer

Pierre Castadot, MD, John A. Lee, Eng, PhD, Xavier Geets, MD, PhD, and Vincent Grégoire, MD, PhD, FRCR

Intensity-modulated radiation therapy (IMRT) in head and neck (H&N) cancer has the capability to generate steep dose gradients, leading to an improved therapeutic index. IMRT plans are typically based on a pretreatment computed tomography scan that provides a snapshot of the patient’s anatomy. Nevertheless, interfractional patient variations may occur because of setup error and anatomical modifications. Therefore, the accuracy of IMRT delivery for H&N cancer may be compromised during the treatment course, potentially affecting the therapeutic index. In this framework, adaptive radiotherapy is a potential solution, which consists of “the explicit inclusion of the temporal changes in anatomy during the imaging, planning, and delivery of radiotherapy.” Adaptive radiotherapy has brought an additional dimension to the management of patients with H&N cancer and has the potential to counteract the effects of positioning errors and anatomical changes. This article reviews the causes and discusses potential solutions to circumvent the discrepancies between the planned dose and the actual dose received by patients treated for H&N malignancies.

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Radiation therapy (RT) plays a critical role in the current management of patients with head and neck (H&N) cancer. By generating steep dose gradients, intensity-modulated radiation therapy (IMRT) has the ability to conform the dose to target volumes with complex shapes, and to avoid organs at risk (OAR) to a much greater degree than it was possible to do with classical three-dimensional (3D) conformal RT. IMRT maximizes tumor coverage and sparing of OARs,1-5 and thus leads to a potential increase in the therapeutic index. In the current practice of IMRT, treatments are planned on kilovoltage (kV) computed tomography (CT) images taken before the course of treatment. This approach, however, does not take into account potential modifications of the patient's anatomy and positioning during a typical 5-7 week treatment course. The reasons for such changes are multifactorial and may be related to the decrease of tumor and nodal volumes, weight loss, alteration in muscle mass and fat distribution, and fluid shift within the body.6-8 Such modifications may induce subtle or even major changes in the locations, shapes, and sizes of the tumor and OARs. With IMRT, the consequences of anatomical changes that may occur during treatment are more dramatic than in conventional treatments because of the sharp dose gradients between the edges of the target volumes and the critical OARs.9-11 Therefore, highly conformal IMRT plans based on a single planning CT dataset may lead to unexpected complications and/or to marginal geographic misses of target volumes, if positional and anatomical uncertainties are not adequately taken into account.

Adaptive RT is a possible solution to overcome these limitations. It consists of “the explicit inclusion of the temporal changes in anatomy during the imaging, planning, and delivery of RT.”12 The purpose of this article is to review the techniques of adaptive RT and discuss their potential for the maximization of the therapeutic index. In the first part, positioning errors and their causes will be presented together with the strategies that could be adopted to counteract setup uncertainties. In the second part, anatomical modifications...
occurring during the treatment course and their potential dosimetric consequences will be reviewed. Different adaptive strategies will then be discussed.

**Positioning Errors and Adaptive Radiotherapy**

Although patients with H&N cancers treated by RT are typically immobilized on the table couch with various devices, patient motion throughout the treatment has been reported.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\)\(^,\)\(^4\)\(^,\)\(^5\)\(^,\)\(^6\)\(^,\)\(^7\)\(^,\)\(^8\)\(^,\)\(^9\)\(^,\)\(^10\)\(^,\)\(^11\)\(^,\)\(^12\)\(^,\)\(^13\)\(^,\)\(^14\) Previously, published data from our institution have reported a setup variability of 2-5 mm with a standard immobilization mask.\(^1\)\(^5\) With radiation techniques providing sharper dose gradients, such as IMRT, set-up uncertainties may lead to a theoretically higher risk of inaccuracy in the dose distribution to target volumes and/or OARs.\(^1\)\(^6\)\(^,\)\(^1\)\(^7\)\(^,\)\(^1\)\(^8\)\(^,\)\(^1\)\(^9\) In this context, image-guided radiotherapy (IGRT), defined as the use of on-board imaging to improve patient setup accuracy, intends to improve the precision of radiation delivery. Various IGRT solutions have been proposed allowing a 3D volumetric reconstruction of the patient anatomy and offering the possibility of online correction of tumor position errors before treatment.\(^1\)\(^8\)\(^-\)\(^2\)\(^0\) Moreover, with the conversion of Hounsfield unit into electron density map, IGRT provides a potential solution for daily dose recalculation making it possible to get the “image du jour” dosimetry.\(^2\)\(^1\)\(^-\)\(^2\)\(^3\) These IGRT solutions include in-room kVCT,\(^2\)\(^4\) kV or megavoltage (MV) cone-beam CT,\(^2\)\(^5\)\(^-\)\(^2\)\(^8\) and helical MVCT.\(^2\)\(^9\)\(^,\)\(^3\)\(^0\) Recent efforts have centered on repeated per-treatment CT imaging.\(^3\)\(^1\)\(^-\)\(^3\)\(^6\) It has been reported that both online and offline adjustments of setup errors could reduce interpatient and interfractional variations. The benefit of offline protocols is however smaller compared with that of online protocols.\(^3\)\(^7\)\(^-\)\(^3\)\(^8\)\(^,\)\(^3\)\(^9\)\(^,\)\(^4\)\(^0\)\(^,\)\(^4\)\(^1\)\(^,\)\(^4\)\(^2\) de Boer et al\(^3\)\(^8\) reported in 31 H&N patients that the use of an offline two-dimensional shrinking action level correction protocol reduced the systematic errors from 1.6-2.1 mm to 1.1-1.2 mm, whereas random errors reached 1.6-1.4 mm. Similarly, van Lin et al\(^3\)\(^9\) reported that for an offline correction protocol for H&N cancer, the systematic errors were reduced from 2.2-2.3 mm to 0.8-1.4 mm, whereas random errors reached 1.5-1.9 mm. Online correction provides the advantage of reducing both the systematic and random errors, whereas an offline protocol can only reduce the systematic error.\(^3\)\(^5\)\(^,\)\(^3\)\(^6\)\(^,\)\(^3\)\(^8\)\(^,\)\(^3\)\(^9\)\(^,\)\(^4\)\(^0\)\(^,\)\(^4\)\(^1\)\(^,\)\(^4\)\(^2\)

The benefit of online correction was notably reported by Han et al,\(^4\)\(^3\) who evaluated the impact of daily helical MVCT-guided setup correction on dose variations to the parotid glands and the spinal cord during IMRT. Compared with the results with daily setup correction, the median dose to the parotids and the daily maximum dose to the spinal cord both increased significantly when daily corrections were not applied. O’Daniel et al\(^4\)\(^4\) designed a study to quantify the differences between planned and delivered doses to parotid glands and target volumes, and to assess the dosimetric benefits of daily CT-based image guidance for H&N cancer patients treated with IMRT. When 3D image-guidance was not used, an increase in the mean parotid dose above the planned dose was observed for both the homolateral (median increase of 3 Gy) and the heterolateral (median increase of 1 Gy) parotids. The use of 3D CT-based image guidance reduced the mean parotid dose in 91% of patients. However, the parotid doses resulting from bone alignment correction was still greater than the planned doses because of anatomical modifications in the soft tissues. None of these approaches affected the tumor dose coverage.

Wang et al\(^4\)\(^5\) evaluated the effect of online cone beam CT-guidance in IMRT for nasopharyngeal tumors. The systematic and random setup errors, as well as planning target volume (PTV) margins, were calculated at different correction levels. In this study, the PTV margin on the basis of correction uncertainties was about 5-6 mm. When online corrections were applied, the PTV margin could be reduced to 3 mm. The effect of online setup correction on dose distribution was simulated. A translational isocenter shift of 3 mm showed that if no correction were applied, the maximum dose to both the brainstem and spinal cord would have been increased by 10 Gy, implying that online correction could provide protection of the spinal cord and brainstem by avoiding overdosing resulting from positioning errors. Similarly, the mean dose to the left and right parotid glands would have been increased by 7.8 and 8.5 Gy, respectively, and the dose to the target volumes would have been decreased by 4 Gy in 95% of the gross tumor volume (GTV) and by 5.6 Gy in 95% of the clinical target volume (CTV).

Classical models of interfractional patient variation have been based on population-based data and not on individual patient-based data. CTV-to-PTV margins are statistically characterized by using the so-called van Herk’s formula for generic planning target margin written as \(2.5 \times \Sigma_{(\mu)} + 0.7 \times \text{RMS}_{(\sigma)}\), which ensures that 90% of the patients receive a minimum dose of 95% to the CTV (\(\Sigma_{(\mu)}\) is the standard deviation of all patients’ systematic set-up errors, \(\text{RMS}_{(\sigma)}\) represents the population’s random deviation and is obtained by calculating the root mean square of all patients’ random deviations).\(^4\)\(^6\)

A more refined model with 4 statistical parameters can also be used to define PTV margin and is based on individual patient-specific setup error.\(^4\)\(^1\) This model provides more intrinsic information to guide the management of interfractional patient variation with multi-images feedback. If the individual patient specific systematic variation and random variation can be estimated and integrated into this patient-based margin design, then we obtain the patient-specific margin distribution. However, this requires us to develop a method to evaluate patient-specific systematic variation and random variation, before or early in treatment. The most common methods to manage patient-specific variation so far use multiple-images feedback to perform a patient-specific target position correction and treatment planning modification. Multiple CT imaging, including on-board cone-beam CT, helical MVCT, and off-board conventional CT scans, combined with treatments is a possible process to adapt the treatment plan and dose distribution design to patient-specific variations. The assumption that underlies the concept of adaptive RT in IGRT is that the CTV-to-PTV margins could
be significantly adapted to the patient-specific setup error during the treatment course using multiple image feedback management in the routine treatment process. The adaptive RT technique aims to customize the treatment plan to patient specific variations by evaluating and characterizing the systematic and random patient specific variations through image feedback and including them in adaptive planning.

Another possible adaptive strategy is to quantify the dosimetric errors that are induced by setup error and to optimize the treatment by taking into account those dosimetric errors. This strategy aims at adaptation of each treatment fraction by taking into account the dose distribution accumulated over the entire course of treatment and the information gathered just before treatment. The goal is, therefore, to adjust the originally prescribed dose to completely compensate voxels, which were overdosed (or underdosed) in previous fractions by decreasing (or increasing) the dose goal at those voxels.47,48 All these reoptimization procedures share the same basic properties; a dosimetric error is introduced during the execution of the original optimal plan because of positioning errors and then the original plan may be modified by reoptimization on the basis of information gathered during a previous execution to compensate the previous suboptimality.49 It is important to note that from a practical point of view, this adaptive strategy is only possible with being able to reconstruct the actual dose distribution using 3D on-board imaging that are designed to perform dose reconstruction.

In summary, online correction strategies using IGRT can be adopted to increase the accuracy of IMRT in H&N cancer by minimizing the detrimental effects of both systematic and random positional errors. The development of on-board 3D volume imaging modalities has offered the possibility of daily imaging and subsequent online correction of tumor position errors before treatment. Thus, modern 3D image-guidance techniques open the avenue toward adapted patient-tailored PTV margins and allow the estimation and possible adaptation to the actual induced dose errors, creating room for further dose escalation without impairing the therapeutic index.

Anatomical Modifications and Adaptive Radiotherapy

Anatomical Modifications of Target Volumes and Organs at Risk During Radiation Therapy

Many patients receiving fractionated RT for H&N cancer show marked anatomical changes during the course of their treatment. These include the shrinkage of the primary tumor and nodal volumes, resolving postoperative changes or edema, and weight loss. The published data contains only a small number of publications that deal with volume variations for H&N cancer patients undergoing external beam RT. These data are summarized in Table 1.

Barker et al6 conducted a pilot study to quantify the magnitude of the anatomical changes using an integrated CT-linear accelerator system. They concluded that GTVs decreased throughout the course of RT, at a median rate of 1.8% per treatment day. On the last day of treatment, this corresponded to a median total relative loss of 69.5% of the initial GTV. In addition, the center of mass of the GTV changed position with time, indicating that tumor loss was frequently asymmetric. At treatment completion, the median center of mass displacement was 3.3 mm. Parotid glands also decreased in volume by 0.6% per treatment day and shifted medially (median shift of 3.1 mm) with time. This medial displacement of the parotid glands correlated with the weight loss that occurred during treatment.

Geets et al50 assessed the modifications in target volumes and in dose distribution during concomitant chemoradiotherapy for 10 patients with locally–advanced squamous cell carcinoma treated with helical tomotherapy. CT scans were acquired for each patient before the treatment started and during RT after mean doses of 14, 25, 35, and 43 Gy. GTVs were manually delineated on CT. From these volumes, CTVs and PTVs were derived using consistent guidelines. The GTVs significantly decreased throughout the course of RT, and it translated into parallel reductions of the corresponding CTVs and PTVs (Fig. 1). Han et al51 focused on parotids using helical MVCT and noted a significant volume change for most parotids during the RT course. At the end of the treatment, the average parotid gland volume had decreased from 20.5 to 13.2 cm$^3$, with an average decrease rate of 0.21 cm$^3$ per treatment day or 1.1% per treatment day. Vasquez Osorio et al52 looked at the 3D anatomical changes of tumors, irradiated or spared parotids, and submandibular glands by performing CT scan analysis at 0 and 46 Gy. They showed that the primary tumor volume shrunk by 25% ± 15% compared with its original volume; irradiated and spared parotid glands had a volume loss of 17% ± 7% and 5% ± 4%, respectively; corresponding figures reached 20% ± 10% and 11% ± 7% for irradiated and spared submandibular glands, respectively. The superficial and inferior regions of the irradiated parotid glands moved inward and posteriorly by an average of 3 mm, and the medial regions tended to remain in the same position. The irradiated submandibular glands shrank and shifted upward, medially, and posteriorly by 4 mm. The spared glands showed only a small deformation.

Hansen et al53 performed a study on 13 H&N cancer patients treated with IMRT. Planning CT scans were performed before treatment and after an average dose of 36 Gy. A mean reduction in the parotid volume of 21.5% and 15.6% was observed for the left and right gland, respectively. Surprisingly, no changes were observed for the GTV. Rohrer et al54 imaged 15 patients weekly using diagnostic CT during the RT course and calculated 3D displacements for several anatomical structures (eg, brainstem, first and sixth cervical vertebrae, second thoracic vertebra, spinal cord, and superficial and mediastinal aspects of the parotid glands). The superficial regions of both parotid glands showed a medial translation of 0.91 ± 0.9 and 0.78 ± 0.13 mm/wk for the left and right parotid, respectively, and overall the parotid glands shrank by 4.9% per week.

We (Castadot et al, unpublished data) studied the volumetric and positional modifications of target volumes and
OARs during the course of concomitant chemoradiotherapy in a series of 10 patients with pharyngolaryngeal squamous cell carcinomas imaged weekly with a diagnostic CT. All CT images were registered using a deformable registration algorithm. The pretreatment CT was registered to any of the per-treatment CT. Deformable registration produced a vector field that mapped any volume element in the reference anatomy (e.g., the pretreatment planning CT) to the corresponding volume element in each per-treatment CT. These data showed (1) a mean relative shrinkage of the primary tumor GTV and nodal GTV of 3.2% per treatment day and 2.1% per treatment day, respectively (Fig. 2); (2) a mean relative shrinkage of the homolateral and heterolateral parotids of 0.9% per treatment day and of 1.0% per treatment day, respectively; (3) a mean relative shrinkage of the prophylactic homolateral and heterolateral nodal CTV (CTVN) of 0.5% per treatment day and of 0.4% per treatment day, respectively. Moreover, the positional analysis showed that after 5 weeks of treatment, (1) the homolateral parotid gland had moved medially by 3.4 mm, (2) the GTV had moved laterally by 1.3 mm, (3) the homolateral and heterolateral parotids had moved medially by 3.1 mm, and (4) the prophylactic nodal CTV had moved medially by 1.8 mm.

Table 1 Anatomical Modifications During Radiation Therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Per-Treatment Imaging</th>
<th>Image Registration</th>
<th>Volume Analysis</th>
<th>Shape and Positional Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barker et al (2004)96</td>
<td>14</td>
<td>In-room CT-on-rail 3 times/wk; no iv contrast</td>
<td>Rigid</td>
<td>Reduction of:  ● GTV: 1.8% per treatment day  ● PGs: 0.6%/treatment day</td>
<td>● GTV: COM displacement: 3.3 mm (asymmetric shrinkage)  ● PG: COM shift medially by 3.1 mm</td>
</tr>
<tr>
<td>Geets et al (2007)50</td>
<td>10</td>
<td>CT scan at mean doses of 14, 25, 35, and 45 Gy; iv contrast</td>
<td>Rigid</td>
<td>After a mean dose of 45 Gy:  ● GTV: mean decrease of 65.5%  ● High dose CTV: mean decrease of 50.9%  ● High dose PTV: mean decrease of 47.9%</td>
<td>NA</td>
</tr>
<tr>
<td>Han et al (2008)43</td>
<td>5</td>
<td>Daily helical MVCT</td>
<td>Rigid</td>
<td>At the end of treatment: PGs had decreased from 20.5 to 13.2 cm³, i.e., an average decrease of 0.21 cm³/treatment day or 1.1%/treatment day</td>
<td>NA</td>
</tr>
<tr>
<td>Vasquez Osorio et al (2008)51</td>
<td>10</td>
<td>CT scan at 46 Gy; iv contrast</td>
<td>Deformable</td>
<td>Reduction after 46 Gy:  ● GTV: 25 ± 15%  ● Homolateral PG: 17 ± 7%  ● Heterolateral PG: 5 ± 4%  ● Homolateral SMG: 20 ± 10%  ● Heterolateral SMG: 11 ± 7%</td>
<td>After 46 Gy:  ● Lateral and inferior regions of homolaterals PG: medial and posterior shift (3 mm)  ● Homolateral SMG: medial, cranial, and posterior shift (4 mm)</td>
</tr>
<tr>
<td>Hansen et al (2006)52</td>
<td>13</td>
<td>CT scan after a mean dose of 38 Gy</td>
<td>Rigid</td>
<td>Reduction:  ● GTV: no change  ● Right PG: 15.6%  ● Left PG: 21.5%</td>
<td>NA</td>
</tr>
<tr>
<td>Robar et al (2007)53</td>
<td>15</td>
<td>Weekly CT scans; no iv contrast</td>
<td>Rigid</td>
<td>Reduction of superficial regions of both PGs: 4.9%/wk</td>
<td>Superficial regions showed medial translation: left PGs: medial shift of 0.91 ± 0.9 mm/wk right PGs: medial shift of 0.78 ± 0.13 mm/wk After 5 treatment wks:  ● Homolateral PG: medial shift of 3.4 mm  ● GTV: lateral shift of 1.3 mm  ● GTVN: medial shift of 0.9 mm  ● Low dose homolateral CTVN: medial shift of 1.8 mm No shift for the heterolateral PG and heterolateral low dose CTVN</td>
</tr>
</tbody>
</table>
| Castadot et al (2008)       | 10              | CT scan at mean doses of 14, 25, 35, and 45 Gy; iv contrast | Deformable        | Reduction of  ● GTV: 3.2%/treatment day  ● GTVN: 2.1%/treatment day  ● Homolateral PG: 0.9%/treatment day  ● Heterolateral PG: 1.0%/treatment day  ● Low dose homolateral CTVN: 0.5%/treatment day  ● Low dose heterolateral CTVN: 0.4%/treatment day | }

CT, computerized tomography; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; PG, parotid gland; COM, center of mass; MV, mega-voltage; SMG, submandibular gland; homolat, homolateral; heterolat, heterolateral; CTV, primary tumor CTV; PTV, primary tumor PTV; CTVN, nodal CTV; GTV, primary tumor GTV; GTVN, nodal GTV; NA, not applicable.
mm, (3) the GTV₅ had moved medially by 0.9 mm, and (4) the prophylactic CTV₅ had moved medially by 1.8 mm. No statistically significant shift was observed for the heterolateral parotids and the heterolateral prophylactic CTV₅.

In summary, RT induces major volumetric and positional changes in CTVs and OARs during treatment. For parotid glands, studies consistently reported a systematic medial shift into the high dose region and significant volume shrinkage, potentially jeopardizing parotid sparing.

Dosimetric Impact of Anatomical Modifications

Because of alteration in patient anatomy during treatment leading to modifications of both target volumes and OARs, the dose distribution that is actually delivered to the patient might significantly differ from what was planned. This could have an adverse effect on the treatment outcome, in terms of tumor control and/or normal tissue complications. With image-guidance techniques becoming more widely available, the dosimetric consequences of the anatomical changes have been reported (Table 2).

O’Daniel et al⁴⁴ designed a study to quantify the differences between planned and delivered parotid dose over the RT course using in-room CT scanner. Modifications in the anatomy of the patient led to increase in the mean parotid dose above the planned dose by a median of 1.0 Gy. No effect on tumor coverage was observed. In Hansen’s study,³² 13 patients were treated with IMRT and had repeated CT imaging during the course of RT. For both therapeutic and prophylactic PTVs, the mean dose to 99% of the volume (D₉₉), the mean dose to 95% of the volume (D₉₅), and the mean percentage of the volume receiving more than 93% of the prescribed dose (V₉₃%), all decreased. Moreover, the doses to OARs also increased, that is the percentage of volume of the right parotid receiving more than 26 Gy (V₂₆Gy) and the percentage of volume of the mandible receiving more than 60 Gy (V₆₀Gy). In Robar’s study,⁵³ for each patient, the IMRT dose distribution was recalculated on each CT image set to determine the dosimetric consequences of anatomical modifications. For the left and right parotids, the mean doses increased by 2.6% ± 4.3% and 0.2% ± 4.0%, respectively. The volume that received 26 Gy increased by 3.5% ± 5.2% for the left gland and 0.3% ± 4.7% for the right gland. Han et al⁵⁴ also evaluated the significance of daily image guidance patient setup corrections by evaluating daily dose variations using helical MVCTs. The mean daily median parotid doses increased from 0.83 to 1.42 Gy with an average increase rate of 0.017 Gy per treatment day, corresponding to an average increase of 2.2% per treatment day. There was a strong correlation between the volume and the median parotid dose during the treatment (correlation coefficient of −0.95). Lee et al⁵⁵ analyzed the changes in parotid dose resulting from anatomical modifications throughout a RT course in a cohort of 10 H&N cancer patients treated by helical tomotherapy. They reported that the daily mean doses differed from the plan dose by an average of 15%. The planned average Dmean of the 20 parotid glands was 29.7 Gy, whereas the average of the cumulative parotid gland Dmean at the end of the treatment reached 32.7 Gy (corresponding to an increase of 10%). The changes in the distance between the centers of mass of the left and right parotid glands correlated significantly with the mean parotid dose changes (R² = 0.88). There was also a correlation between the relative weight loss and higher mean parotid doses (R² = 0.58). In our series of 10 patients discussed earlier in the text, the vectors fields generated from the nonrigid deformation of the various sets of images were applied on the dose maps to reconstruct the dose distribution from the per-treatment CT on the pretreatment CT. Doses could then be added to get the composite dose distribution actually delivered to patients. This method allowed the comparison of the cumulative dose distribution to the planned ones on a unique reference set of images (Table 3, second column). The doses actually delivered to the parotid and submandibular glands, the oral cavity, the spinal cord, the planning at risk volume for the spinal cord, and the skin were substantially increased compared with the planned doses. An increased delivered dose was also observed in the volumes that received high doses, for example, V₁₀₀%, V₉₅%, V₉₀%.

Figure 2 Volumetric changes in the primary tumor gross tumor volume (GTV) during treatment of pharyngolaryngeal tumors. (Color version of figure is available online.)
In summary, without any replanning, the dose delivered to OARs and normal tissues are significantly increased during typical treatment for H&N tumors. Thus, repeated image acquisitions during the course of IMRT for patients with H&N cancer may become essential to identify volumetric changes with potential dosimetric consequences. In particular, it appears that parotid glands are at significant risk to get a higher dose than planned because of a medial shift towards the high isodose volumes. However, the magnitude of the dosimetric consequences of the anatomical changes depends on several variables, including the location of the target volumes with a high prescribed dose, the proximity of the OARs to the high-dose region, and the local dose gradient.

Table 2 Dosimetric Effect of Anatomical Modifications During Radiation Therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Per-Treatment Imaging</th>
<th>Image Registration</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Daniel et al (2007)</td>
<td>11</td>
<td>In-room CT-on-rail scans twice/wk; no iv contrast</td>
<td>Deformable</td>
<td>Cumulative PG dose greater than planned; median dose increase: 1 Gy No impact on tumor dose coverage</td>
<td>If no image-guidance for daily setup error correction, cumulative PG dose greater than planned; median dose increase: 3 Gy for homolat PG and 1 Gy for heterolat PG</td>
</tr>
<tr>
<td>Hansen et al (2006)</td>
<td>13</td>
<td>CT scan after a mean dose of 38 Gy</td>
<td>Rigid</td>
<td>High dose PTV D99, D95, V93% decreased by 12.1, 12.2 Gy, and 7%, respectively Low dose PTV D99, D95, V93% decreased by 12.6, 11.3 Gy, and 8.2%, respectively Right PG V26Gy increased by 10.9% Mandible V60Gy increased by 7.2%</td>
<td>If replanning: significant improvement of: Low and high dose PTVs D99 D95 and V93% Spinal cord Dmax, D1cc Brainstem Dmax Right parotid PG Dmean, D50, and V26Gy Mandible Dmax and V60Gy</td>
</tr>
<tr>
<td>Robar et al (2007)</td>
<td>15</td>
<td>Weekly CT scan; no iv contrast</td>
<td>NA</td>
<td>Left PG Dmean increased by 2.6 ± 4.3%, V26Gy increased by 3.5 ± 5.2% Right PG Dmean increased by 0.2 ± 4.0%, V26Gy increased by 0.3 ± 4.7%</td>
<td>If replanning; significant improvement of: Low and high dose PTVs D99 D95 and V93% Spinal cord Dmax, D1cc Brainstem Dmax Right parotid PG Dmean, D50, and V26Gy Mandible Dmax and V60Gy</td>
</tr>
<tr>
<td>Han et al (2008)</td>
<td>5</td>
<td>Daily helical MVCT</td>
<td>Rigid</td>
<td>PG Dmedian increased from 0.83 to 1.42 Gy with an average increase rate of 0.17 Gy/treatment day corresponding to an average increase of 2.2%/treatment day Strong correlation between the volume and the median parotid dose during the treatment (correlation coefficient, −0.95)</td>
<td>If replanning: significant improvement of: Low and high dose PTVs D99 D95 and V93% Spinal cord Dmax, D1cc Brainstem Dmax Right parotid PG Dmean, D50, and V26Gy Mandible Dmax and V60Gy</td>
</tr>
<tr>
<td>Lee et al (2008)</td>
<td>10</td>
<td>Daily helical MVCT</td>
<td>Deformable</td>
<td>PG daily Dmean differed from the planned dose by an average of 15% PG cumulative Dmean; planned: 29.7 Gy actual: 32.7 Gy (110% of planned dose) Changes in the distance between the COMs of the left and right PGs correlated strongly with the mean parotid dose changes (R² = 0.88) Correlation between the relative weight loss and higher parotid mean doses (R² = 0.58)</td>
<td>If replanning; significant improvement of: Low and high dose PTVs D99 D95 and V93% Spinal cord Dmax, D1cc Brainstem Dmax Right parotid PG Dmean, D50, and V26Gy Mandible Dmax and V60Gy</td>
</tr>
<tr>
<td>Castadot et al (2009)</td>
<td>10</td>
<td>CT scan at mean doses of 14, 25, 35, and 45 Gy; iv contrast</td>
<td>Deformable</td>
<td>PGs Dmean; planned: 17.9 Gy, actual 18.7 Gy SMGs Dmean; planned 51.9 Gy, actual: 52.8 Gy OC Dmean; planned 26.0 Gy, actual 26.7 Gy SC D2; planned 40.1 Gy, actual: 41.0 Gy Skin V60; planned 17.2 Gy, actual 18.3 Gy No difference in PTV or CTV coverage</td>
<td>If replanning; significant improvement of: Low and high dose PTVs D99 D95 and V93% Spinal cord Dmax, D1cc Brainstem Dmax Right parotid PG Dmean, D50, and V26Gy Mandible Dmax and V60Gy</td>
</tr>
</tbody>
</table>

OC, oral cavity; SC, spinal cord; Dx, dose to x% of the volume; Dmax, maximum dose; D1cc, dose to 1 cc.; Dmean, mean dose; Dmedian, dose to 50% of the volume; Vx, volume receiving a dose of x Gy or x% of the prescribed dose.

the O’Daniel study, anatomical modifications did not induce deterioration of the therapeutic or prophylactic CTVs or PTVs coverage.

In summary, without any replanning, the dose delivered to OARs and normal tissues are significantly increased during typical treatment for H&N tumors. Thus, repeated image acquisitions during the course of IMRT for patients with H&N cancer may become essential to identify volumetric changes with potential dosimetric consequences. In particular, it appears that parotid glands are at significant risk to get a higher dose than planned because of a medial shift towards the high isodose volumes. However, the magnitude of the dosimetric consequences of the anatomical changes depends on several variables, including the location of the target volumes with a high prescribed dose, the proximity of the OARs to the high-dose region, and the local dose gradient.
Replanning During the Treatment Course

As discussed above, several studies have reported that due to modifications of the patient anatomy during treatment, the dose actually delivered was higher than the planned dose. This observation raised the question of adaptive replanning treatment for H&N patients. Although much effort is concentrated on such strategy, very few data have been reported so far.

Mohan et al\(^57\) reported a method for modifying IMRT plans and treatment parameters to account for interfraction changes in positions, volumes, and shapes of anatomical structures. The method involves deformation of the dose distributions of the IMRT plan based on the deformation of the patient anatomy imaged with CT-on-rail on the treatment day just before the actual delivery of the current fraction. Dose intensity distributions were adapted for each beam based on the deformation of structures seen in the beam’s-eye-view. This process involved daily CT imaging, online near real-time modification of the IMRT plan, including complete replanning if indicated, and the plan delivery without moving the patient. They compared the results obtained with this strategy to the corresponding data derived (1) from the pretreatment plan applied to the original image, (2) from the pretreatment plan applied to the daily on-board images, and (3) from a new full-fledged IMRT plan designed based on the daily images. Dose intensity distributions were adapted for each beam based on the deformation of structures seen in the beam’s-eye-view. This process involved daily CT imaging, online near real-time modification of the IMRT plan, including complete replanning if indicated, and the plan delivery without moving the patient. They compared the results obtained with this strategy to the corresponding data derived (1) from the pretreatment plan applied to the original image, (2) from the pretreatment plan applied to the daily on-board images, and (3) from a new full-fledged IMRT plan designed based on the daily images. The coverage of the primary target volumes and involved lymph nodes, and the sparing of the parotids were essentially identical for the reoptimized plan and the deformed intensities plan, whereas the application of the original plan led to poor coverage (85.4% and 89.5% for the primary tumor volume and the lymph nodes, respectively). Application of the original plan led to poor coverage (85.4% and 89.5% for the primary tumor volume and the lymph nodes, respectively).

Hansen et al\(^52\) not only studied the volumetric effect on the parotids and the dosimetric modifications, but also studied the possible effect of a replanning based on CT scans acquired during the treatment. Replanning improved the D\(_{99}\), D\(_{95}\), and V\(_{93}\)\% for both the therapeutic and prophylactic PTVs. Moreover, the replanning strategy significantly improved the dose distribution to the OARs, ie, (1) the spinal cord D\(_{max}\) and dose to 1 cc. of the volume, (2) the brainstem D\(_{max}\) (3) the right parotid gland D\(_{mean}\), D\(_{50}\), and V\(_{26}\)Gy, and (4) the mandible D\(_{max}\) and V\(_{60}\)Gy. In other words, replanning could compensate for dosimetric degradations caused by anatomical modifications during treatment.

Kuo et al\(^58\) studied the effect of the regression of enlarged neck lymph nodes on the dose to the parotids during an IMRT course by repeating a CT scan after a dose of 45 Gy. The remaining dose of 21 Gy was then delivered after a second plan was performed to reflect the change in the nodal tumor volume. Enlarged neck lymph nodes in all patients pushed the parotids outward in pretreatment CT images. After a dose of 45 Gy, nodal regression caused the parotids to shift inward into the high-dose area. When compared with the no-replanning scenario, the parotid glands dose was significantly reduced by 2.9 and 3.2 Gy for the left and right parotid, respectively.

Geets et al\(^50\) assessed the effect on dose distribution of replanning based on weekly imaging with diagnostic CT scan during concomitant chemo-RT (Fig. 3). Treatment plans were adapted based on the changing primary tumor volumes.

### Table 3 Comparison Between the Planned Doses, the Actually Delivered Doses Without Replanning, and the Actual Doses if Adaptive Plannings Were Performed

<table>
<thead>
<tr>
<th></th>
<th>Planned Dose (Gy)</th>
<th>Actually Delivered Dose (Gy)</th>
<th>Re-planned Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organs at risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parotid glands D(_{mean})</td>
<td>17.9</td>
<td>18.7</td>
<td>18.7</td>
</tr>
<tr>
<td>Submandibular glands D(_{mean})</td>
<td>51.9</td>
<td>52.8</td>
<td>51.7</td>
</tr>
<tr>
<td>Oral cavity D(_{mean})</td>
<td>26.0</td>
<td>26.7</td>
<td>24.4</td>
</tr>
<tr>
<td>Spinal cord D(_{2})</td>
<td>40.1</td>
<td>41.0</td>
<td>39.1</td>
</tr>
<tr>
<td>Planning at risk volume around spinal cord D(_{2})</td>
<td>42.3</td>
<td>44.2</td>
<td>41.2</td>
</tr>
<tr>
<td>Larynx D(_{5})</td>
<td>67.9</td>
<td>67.7</td>
<td>67.7</td>
</tr>
<tr>
<td>Skin V(_{60})(\text{ Gy})</td>
<td>17.2</td>
<td>18.3</td>
<td>16.3</td>
</tr>
<tr>
<td><strong>Target volumes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic CTV D(_{95})</td>
<td>68.4</td>
<td>68.4</td>
<td>65.3</td>
</tr>
<tr>
<td>Therapeutic PTV D(_{95})</td>
<td>66.6</td>
<td>66.6</td>
<td>62.0</td>
</tr>
<tr>
<td>Prophylactic CTV D(_{95})</td>
<td>54.9</td>
<td>54.9</td>
<td>55.2</td>
</tr>
<tr>
<td>Prophylactic PTV D(_{95})</td>
<td>54.1</td>
<td>54.0</td>
<td>54.3</td>
</tr>
<tr>
<td><strong>Irradiated volumes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned irradiated volume (cc)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actually irradiated volume (cc)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Replanned irradiated volume (cc)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V(_{100})%</td>
<td>140.4</td>
<td>150.2</td>
<td>112.1</td>
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<tr>
<td>V(_{95})%</td>
<td>246.5</td>
<td>261.4</td>
<td>202.0</td>
</tr>
<tr>
<td>V(_{90})%</td>
<td>274.7</td>
<td>323.1</td>
<td>261.0</td>
</tr>
</tbody>
</table>

Kuo et al\(^58\) studied the effect of the regression of enlarged neck lymph nodes on the dose to the parotids during an IMRT course by repeating a CT scan after a dose of 45 Gy. The remaining dose of 21 Gy was then delivered after a second plan was performed to reflect the change in the nodal tumor volume. Enlarged neck lymph nodes in all patients pushed the parotids outward in pretreatment CT images. After a dose of 45 Gy, nodal regression caused the parotids to shift inward into the high-dose area. When compared with the no-replanning scenario, the parotid glands dose was significantly reduced by 2.9 and 3.2 Gy for the left and right parotid, respectively.

Geets et al\(^50\) assessed the effect on dose distribution of replanning based on weekly imaging with diagnostic CT scan during concomitant chemo-RT (Fig. 3). Treatment plans were adapted based on the changing primary tumor volumes.
A composite plan was then computed by adding-up the doses on the reference pretreatment CT. The adaptive IMRT planning reduced the volume receiving high doses compared with pretreatment CT planning ($V_{90\%}$, $V_{95\%}$, and $V_{100\%}$ reduced by 15%, 20%, and 34%, respectively). In that study, rigid registration could only be used, and only modifications in the primary tumor volumes could be taken into account. Consequently, the effect of such strategy on the OARs could not be properly assessed. The data were recently reprocessed using deformable registration algorithm to compute the modifications in dose distribution throughout the images (Castadot et al, unpublished data). In this study, reoptimization was performed on each of the per-treatment planning CT. High dose GTVs and CTVs were delineated on each per-treatment CT images. Prophylactic dose CTVs and OARs were automatically delineated on the per-treatment images using nonrigid deformation of the pretreatment volumes. On each set of images, a CTV to PTV margin of 4 mm was applied. After optimization, all dose distributions were reported back on the pretreatment CT using nonrigid deformations of volumes and doses. This procedure made it possible to sum-up the dose and generate cumulative dose-volume histograms of target volumes and OARs. A preliminary analysis showed that the adaptive strategy allowed recovery of some of the extradose delivered to the submandibular glands, the oral cavity, the spinal cord, the planning at risk volume of the spinal cord, and the volumes receiving a high isodose level (Table 3, third column). A slightly better coverage of the prophylactic CTV was also noticed. On the contrary, doses to the initially delineated therapeutic CTV and PTV showed a decline because of the shrinking target volume strategy adopted in this planning study. Surprisingly, no difference was observed in the mean dose to the parotids. Further analyses of the data are required, but it appears as if only 50% of patients benefited from this approach, thus leveling off the mean parotid dose. Selection of patients who might ultimately benefit for an adaptive treatment will be needed.

One major question arising from adaptive treatment strategy is whether the adaptation of target volumes should also concern the GTV and the related CTV and PTV. Indeed, imaging modalities do have limitation in spatial resolution that affects their sensitivity to detect low tumor burden. It might thus be safer to envisage a strategy where the cone-down in the GTV is used for prescribing an extra boost dose, while conserving the prescribed dose to the original target volumes.

In summary, the primary advantage of adaptive IMRT lies in greater normal tissue sparing with significant improvements in cumulative doses to some OARs. Some useful surrogate criteria or “flags” might however be needed to identify patients who might benefit from an adaptive strategy. A major potential advantage of adaptive strategy is the ability to create adapted plans that could compensate for underdosage of target volumes or overdosage of OARs. However, because of the extra burden for the staff and associated cost, the optimal adaptive strategy still needs to be defined.

Conclusions

Although the concept of adaptive RT has been around for many years, its implementation has been limited until the recent emergence of delivery machine integrating on-board
volumetric-imaging device. The on-board imaging devices provide patient per-treatment 3D images allowing for possible recontouring and replanning. A significant promise of adaptive RT is the compensation of uncertainties, including organ deformation and interfraction patient motion as well as dosimetric errors incurred in previous fractions. This strategy would lead to the delivery of the most conformal and most accurate dose distributions with the potential to further improve patients’ outcome. As a technological innovation, adaptive RT may become the new treatment standard and eventually replace the classical treatment plan in the routine clinical practice. However, adaptive RT remains extremely time-consuming and automation of the different processes involved will be required. There is considerable potential for further improvement in near real-time processes involving 3D CT image acquisition, automated segmentation, deformable registration, and modification of IMRT parameters, possibly including replanning, performed just before the delivery of each fraction. Practical guidelines for identifying patients who would be best served with an adaptive treatment strategy still have to be defined. Prospective studies with larger sample sizes will have to be conducted to address the safety and the clinical effect of such approaches on patient outcome. In the meantime, owing to the complexity of the procedure, adaptive RT should be used in routine clinical practice with caution.

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Adaptive radiotherapy of head and neck cancer

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