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TECHNICAL NOTE

Adaptive Radiotherapy for Head Neck Cancer

Shrikant Balasaheb Mali[1]

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Abstract Changes in patient anatomy may occur either from a tumour volume, position or function of a specific organ at risk, or target volume, weight loss or a reduction in postoperative oedema, and may vary between patients. Adaptive radiotherapy aims to correct morphological variations by realizing one or more plans during the treatment course. Imaging is used to detect these variations, thereby deciding on a potential replanning. At present, adaptive radiotherapy for head neck cancer (HNC) mainly deals with treatment response, such as weight loss or tumor shrinkage. Therefore a properly timed repeat CT scan during treatment is a suitable basis for plan adaptation to account for treatment response.

Keywords Radiotherapy · Adaptive radiotherapy · Head neck cancer · IMRT

Need for Changes in Current Radiotherapy Treatment

Patient's anatomy can vary within a fraction, with swallowing and respiratory motion [1] and from fraction to fraction, with changes in bladder/bowel filling and tumor shrinkage [2]. Anatomy may change due to changes in tumour volume, position or function of a specific organ at risk, or target volume, weight loss or a reduction in postoperative oedema, and may vary between patients. And these changes can lead to an ill-fitting immobilization mask. Skull is attached to a semirigid mandible and to a column of cervical vertebral units with multiple degrees of movement freedom. Larynx represents largest systematic setup uncertainty in head and neck region, because of internal motion secondary to swallowing and tongue movement. Inspiration and expiration also causes displacement of the larynx. Videofluoroscopy can demonstrate 20–25 mm cranialcaudal and 3–8 mm anterior–posterior laryngeal movement during swallowing of liquid [3–5]. Small misalignments, random or systematic, resulting from patient setup, posture or anatomy changes, can significantly influence the position and shape of the dose distribution delivered to the patient. A reduction of geometrical uncertainties allows smaller margins and may increase the therapeutic ratio.

Dosimetric Impact of Anatomical Modifications

Barker et al. [6] reported a 70 % reduction of the gross tumor volumes (GTV) together with substantial changes in the anatomical structures including external neck contour modifications, medial shift of normal structures due to tumor shrinkage, weight loss, and parotid shrinkage. They concluded that GTVs decreased throughout the course of radiotherapy (RT) at a median rate of 1.8 % per treatment day. Similar findings have been reported by Geets et al. [7, 8]. Progressive shrinkage of around 1 % per treatment day and displacement of 3–4 mm by the end of treatment toward the mid-sagittal plane have been consistently reported for ipsilateral parotids. Smaller variations have been noted for the contralateral parotids [9].

Han et al. [10] noted that 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

✉ Shrikant Balasaheb Mali
shrikantmali@gmail.com

[1] MGV KBH Dental College, Flat No 2, Jyoti Savitri Apartment, Above Bank of Maharashtra, Ashoka Marg, Nashik, India

treatment day or 1.1 % per treatment day. Vasquez Osorio et al. [11] 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. Robar et al. [12] reported that the superficial regions of both parotid glands showed a medial translation of 0.91–0.9 and 0.78–0.13 mm/week for the left and right parotid, respectively, and overall the parotid glands shrank by 4.9 % per week.

O'Daniel et al. [13] reported that 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. Han et al. [10] also reported that 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. Lee et al. [14] reported that the daily mean doses differed from the plan dose by an average of 15 %. Studies conducted by Hansen et al. [15] and Zhao et al. [16] found that changes during treatment significantly decreased the dose to target volumes and significantly increased the dose to surrounding organs at risk (OAR) such as the spinal cord and brainstem. Schwartz et al. [17] found significant underdosing of target volumes and increases to parotid gland doses.

Such modifications induce subtle or even major changes in the locations, shapes, and sizes of the tumor and OAR. 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 OAR [18–20]. In HNC bony anatomy is often used as surrogate for the position of the tumor and OAR because lack of contrast and quality in portal images/CBCT scans seldom allow direct identification based on image intensity. Therefore, progressive anatomy changes, such as weight loss or tumor shrinkage, frequently occurring in HNC patients, are hard to capture [21–23].

Adaptive Radiotherapy

Adaptive radiotherapy (ART) is used to correct morphological variations by utilizing one or more plans during the treatment. Imaging is used to detect these variations and change treatment plan accordingly. Adaptive plan modification also take into account imperfections in previously delivered dose distributions, patient-specific estimates of intrafraction motion variability, distinguish favorable and nonfavorable anatomical configurations. Daily adaptive planning requires highly efficient protocols to limit the probability of intrafraction variability that deteriorates plan quality and maintain short treatment slots.

Adaptive radiotherapy is defined as changing the radiation treatment plan delivered to a patient during a course of radiotherapy to account for temporal changes in anatomy (e.g. tumor shrinkage, weight loss or internal motion) and changes in tumor biology/function (e.g. hypoxia). Adaptive radiotherapy is used to refer to different procedures used throughout the course of a treatment to account for anatomical and functional variations that can affect the dose distribution [24]. In this method stationary anatomy is replaced by a variable anatomy, by utilizing daily imaging in the radiotherapy process [25]. This means patients undergo imaging during their radiotherapy course to get new radiotherapy plan based on this new imaging, including changes in anatomy. Modifications of a treatment plan during the treatment is generally made empirically based on weight loss, change in neck separation or poor immobilization shell fit [26].

Investigations of various external predictors for the need to replan, include skin separation and positional variation but single anatomical or positional variable is not a reliable predictor [27, 28]. In contrast, Capelle and colleagues found, when assessing ART using helical tomotherapy in HNSCC patients, that the best predictors of patients receiving the greatest benefit were the degree of weight loss and reduction in neck separation [29]. Triggers used as basic thresholds for ART in the study by Chen et al. [30] included dramatic weight loss, rapid clinical shrinkage of palpable or visible disease and/or a prolonged treatment break. These results are comparable to those of the Brown et al. [26] where it was found that N stage, size of the pre-treatment dominant node, diagnosis and initial weight were significant factors in the likelihood of needing replanning.

Strategies for Adaptive Radiotherapy

Current ART approaches depend on in-room megavoltage CT, CT-on-rails, or cone-beam CTs obtained prior to daily treatment [17]. ART for HNC is concerned with issues such as weight loss or tumor shrinkage. So CT scan during treatment is basis for plan adaptation to account for treatment response. Substantial systematic deformations, up to 3.5 mm, are present with HNC patients [31]. ART is dependent on hardware and software tools, such as on-board imaging, image registration algorithms, image segmentation techniques, and dose summation. Ultimately image guidance should be based on soft tissue structures. ART has three basic components: (1) detection of changes, (2) method of intervention, and (3) management of overall clinical goals. Successful implementation of each component determines the overall success of clinical application. The concept of adaptive planning has been validated [9].

ART can be applied on time scales roughly categorized as (1) off-line, (2) online, and (3) in-line. Typically, off-line adaptive plan modifications are applied once during the treatment course, or even on selected patients whose setups demonstrate large systematic errors. It has been reported that both online and offline adjustments of setup errors could reduce interpatient and interfractional variations. Online correction provides the advantage of reducing both the systematic and random errors, whereas an offline protocol can only reduce the systematic error [18, 32].

de Boer et al. [33] reported in 31 HNC 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. [34] reported that for an offline correction protocol for HNC, 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. In head and neck cancers, anatomical changes are mainly progressive over the treatment course and, therefore, off-line adaptation is probably most realistic, as the immediacy of online adaptation is generally not required [24].

The benefit of online correction was notably reported by Han et al. [10]. Online adaptive protocols aim to account for both interfraction and intrafraction variations. The adaptations could range from adapting only a few machine parameters (e.g., couch position) to a full reoptimization of the treatment plan. Most commonly known adaptation strategies include gating, where the treatment beam is on only when the target is close to the planned position, and tracking, where the treatment equipment is used to maintain a constant target position in the beam's eye view. An interesting alternative to tumor tracking is tumor trailing, where only the time-averaged mean position is followed up to account for possible time trends. Such adaptive protocols require image acquisition sequences with temporal resolution tailored to the time scale of the intrafraction variability [32]. Wang et al. [35] reported that online correction could provide protection of the spinal cord and brainstem by avoiding overdosing resulting from positioning errors. Online adaptive protocols will typically be applied daily, and they not only use the image information of previous fractions to adapt the treatment plan but also an image acquired during the fraction itself. Online protocols thus have the ability to correct for interfraction day-to-day variations.

Replanning

Different authors [2, 6, 13, 36–40] have studied replanning strategies. They have reported that one adaptive replanning during midcourse improved parotid mean dose sparing by 3 %, two replannings by 5 %, and six replannings by 6 %. 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. In other words, replanning could compensate for dosimetric degradations caused by anatomical modifications during treatment. Several authors [2, 10, 38] found that without replanning, tumor coverage and dosimetry decreases whereas at the same time spinal cord dose is increased by up to 10 %. Hansen et al. [2] reported that in the absence of adaptive replanning, there was a significant reduction in planning target volume PTV coverage.

Wang et al. [35] reported that significant benefits to replanning were found in clinical tumor volume CTV1 V100 and nodal GTV V100 (increased 4.9 and 1.8 %, respectively); and spinal cord point maximum, left parotid mean dose and right parotid V30 (decreased 5 Gy, 4.2 Gy and 3.2 %, respectively).

The strength of ART became more obvious by evaluating dosimetry in individual patients than by studying population-averages. Hansen et al. [2] noticed even greater dosimetrical differences in targets and OAR between planning and re-planning in individual cases.

Dosimetric

Another possible adaptive strategy is to quantify the dosimetric errors that are induced by setup error and to reoptimize 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 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 [41, 42].

Imaging in Adaptive Radiotherapy

In-room CT scanners, tomotherapy-based megavoltage CT, and gantry-mounted cone beam CT are now all available to provide in-room 3D imaging. A unique requirement for 3D position verification is selection of a region of interest (ROI) to determine shifts relative to reference simulation images. Image registration requires the development of algorithms that can identify non-rigid (or elastic) deformation [24, 43, 44]. Planning studies have shown that dose adaptation can recover the extra dose delivered to the irradiated volume, and in particular to the parotid glands [14, 45]. It is widely accepted that deformable image registration (DIR) algorithms will play a vital role in ART [18,

24, 46]. The planning CT (pCT) can be deformed to match the daily anatomy (CBCT) for calculating the "dose of the day", the deformation field can be used for automatic recontouring and the daily dose distributions can be warped back to the pCT for dose summation [21].

Local misalignments may be detected with multiple region-of interest (mROI) registration. In mROI registration, a set of sub-regions is rigidly registered. mROI registration has the advantage over single large ROI registration in that alignment of bony structures does not lead to confusing results due to deformations. A single couch correction is therefore always a compromise, leading to residual setup errors. Recent studies with patients with HNC have shown that local misalignments should not be ignored. Ultimately image guidance should be based on soft tissue structures [21–23].

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. IGRT solutions include in-room kVCT, kV or megavoltage (MV) conebeam CT, and helical MVCT [18].

MRI has the potential to provide imaging biomarkers of therapy response of tumor or normal tissue or both. Subsequently, these imaging biomarkers can drive adaptive plan modifications to account for the observed therapy response. The availability of in-room MRI would address the issue of changing hypoxia volumes and locations within tumors and would allow for online dose painting of hypoxic areas if desired. Volume adjustments would be routine as would be individualization of dose, which makes sense given the large variation of tumor size and burden in patients with head and neck cancers, and the biologic differences of individual tumors, as obvious currently in HPVþ vs HPV cases [47]. Adjustments would allow better normal tissues paring, particularly salivary gland sparing.

Conclusion

Adaptive radiotherapy is superior to non-adaptive treatment. The advantages include increase in minimum doses in the target structures and reduction in cumulative maximum dose in dose-painted areas. Current challenges in this area include image quality aspects of online imaging (e.g. conebeam CT), the performance of auto-segmentation algorithms, establishment of relevant and cost-effective treatment decision rules, plan generation strategies and quality assurance procedures. The concept of adaptive RT has also been taken across to the area of biological/functional imaging, with the emerging field of biology-guided adaptive RT. Hypoxia imaging is an important parameter to guide and adapt RT, along with other key radiobiological parameters such as proliferation, cell density and intrinsic radio-resistance. ART implementation involves an increased workload for clinical staff, including Radiation Therapists, Medical Physicists and Radiation Oncologists, and an increased use of departmental resources due to the replanning process.

Compliance with Ethical Standards

Conflict of interest None.

Human and Animal Rights This article does not contain any studies with human participants or animals performed by any of the authors.

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