Curr Oncol Rep (2012) 14:139–147
DOI 10.1007/s11912-012-0221-4

Current Progress in Adaptive Radiation Therapy for Head and Neck Cancer

David L. Schwartz

Published online: 11 February 2012

Abstract Head and neck intensity-modulated radiotherapy (IMRT) remains toxic, and cannot compensate for anatomic changes or tumor response that occur during treatment. Adaptive radiotherapy (ART) is a novel approach to correct for variations in geometry of tumor and bystander anatomy with repeated imaging-based modification of treatment delivery. Technical limitations have hampered introduction of ART into routine practice. This review summarizes investigational challenges impacting development of head and neck ART, describes findings from early clinical testing of an automated ART platform, and highlights emerging directions of ongoing research.

Keywords Adaptive radiotherapy · Head and neck cancer · Image-guided · IMRT · Dosimetry · Clinical trial

Introduction

IMRT planning requires anatomic information obtained by CT or MRI imaging taken days to weeks before treatment. Unfortunately, the geometry of tumor and normal anatomy change significantly during this lag time, and continue to evolve during a 6–7 week course of treatment due to disease response, post-operative healing, and fluctuations in body weight [1–5]. Serial CT imaging taken during head and neck (H&N) treatment demonstrates that primary tumors can shrink by over 90%, and that parotid glands can involute and shift by up to a centimeter during a treatment course [6•].

Recent randomized data have confirmed that the dosimetric advantages of head and neck IMRT over conventional treatment translate into clinically meaningful progress. IMRT reduces parotid toxicity [7]. Nonetheless, no additional benefits beyond this have been confirmed. Much of IMRT's ability to reduce toxicity is potentially wasted if statically guided by pre-treatment imaging.

Further dosimetric advantages may be possible with manual replanning of IMRT midway through treatment [8], although this is typically too time-consuming for routine practice. Adaptive radiotherapy (ART) is a formal approach to correct for daily tumor and normal tissue variations through streamlined online or offline modification of original IMRT target volumes and plans. ART is a decades' old concept, but technical limitations have held back integration of ART into routine care. Older ART approaches have depended largely upon on implanted fiducial markers or ad hoc serial imaging to guide manual replanning. Ideally, staff input should be replaced by automated processes [9–11].

IMRT planning requires accurate targeting of gross tumor [12–16] and normal bystander anatomy [17, 18]. IMRT may be able to limit dysphagia and aspiration through identification of sensitive regions of parotids, larynx, oral cavity, and pharynx [19, 20] and subsequent shielding of these areas [21–23]. As discussed further below, lack of updated targeting during a course of therapy is a likely culprit responsible for continued problems with severe treatment toxicity during and following IMRT. Optimal therapeutic index will ultimately rely on accurate knowledge of setup uncertainties, normal organ dose tolerances, and delineation of treatment targets to minimize planning target volumes (PTVs) while offering safe tumor coverage.

D. L. Schwartz (✉)
Department of Radiation Medicine, North Shore-LIJ Health System,
270-05 76th Avenue,
New Hyde Park, NY 11040, USA
e-mail: dschwartz3@nshs.edu

The Challenge to Improve H&N IMRT: What Do We Need to Adapt To?

Baseline Anatomic Uncertainties

The baseline uncertainties of H&N radiation treatment have long been recognized [24–31]. With the recent availability of kV x-ray units mounted directly onto linear accelerators, it is possible to acquire high-quality images immediately before or even during daily treatment [32]. An advantage of in-room kV imaging is that it provides static 2D images similar to those derived from simulation CTs. However, this method assumes that anatomic landmarks are imaged and measured identically across time, which, of course, is not practical.

In-room CT scanners, tomotherapy-based megavoltage CT, and gantry-mounted cone beam CT are now available to allow treatment machines acquire 3D imaging [33–36]. A unique requirement for 3D position verification is selection of a region of interest (ROI) to determine shifts relative to reference simulation images. This process is particularly complicated for the H&N region due to complex movement relationships between soft and bony tissues. The skull is attached to a semirigid mandible and a flexible column of cervical vertebral units with multiple degrees of freedom [37]. Zhang et al. [38] were the first to use in-room CT imaging and serial 3D image registration to analyze the relative movement of different H&N regions. Three bony ROIs were used for this study: the C2 vertebral body, the C6 vertebral body, and the palatine process of the maxilla as a surrogate for skull base. Displacement uncertainties of up to 6 mm were observed between any two of these ROIs, demonstrating the effects of flexibility and rotation on position uncertainty. In a more recent study [39], H&N subregions were shown to move according to differential flexion. Local residual errors ranged up to 3.4 mm (one standard deviation), translating to a need for up to 7 mm PTV margin expansions.

Anatomic Uncertainties Occurring During Treatment

Most patients will have significant anatomic changes during their course of treatment, including regression of primary tumors or nodal masses, fluctuations of post-surgical edema, and weight loss. An example of such a case is shown in Fig. 1, illustrating how on-treatment anatomical changes can corrupt the geographic precision and clinical intent of the original IMRT plan.

Barker et al. [6•] used serial in-room CT imaging to study gross tumor volume (GTV) changes during a complete course of H&N IMRT. GTV decreased throughout therapy at a median rate of 0.2 cc per treatment day (range, 0.01–1.95 cc/day). On the last day of radiation treatment, this corresponded to a median relative loss of approximately

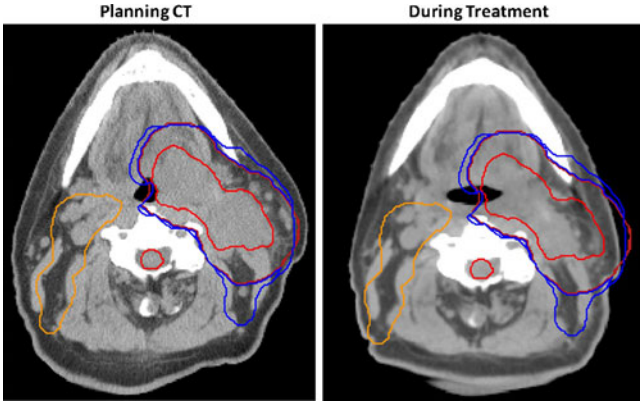

Fig. 1 Anatomic changes can be pronounced during treatment. In this example, planning CT scan and CTV contours are shown on the *left*. On the *right*, a mid-course CT (3 weeks into treatment) demonstrates significant reduction in gross tumor (*thick red line*). Baseline CTVs have been overlaid via rigid image registration. These match current anatomy poorly and in fact extend past the skin contour into air

70% of total original GTV (range, 10%–92%). Rate of volume loss was strongly associated with the baseline target volume, a relationship that could help to identify candidate patients who may benefit most from an adaptive radiotherapy approach.

Parotid glands also grow smaller during therapy. Barker et al. observed that the median parotid volume loss was 0.6%/day from baseline. At the end of treatment, median parotid volume loss was 28.1%. The center of mass of both parotid glands shifted medially over time. By the end of treatment, this medial shift was 3.1 mm (range, −0.3–9.9 mm). Lee et al. [40] acquired similar data using daily megavoltage CT imaging. Day-to-day variations in the center-of-mass distance and volume were 1.61 mm and 4.36%, respectively. Parotid volumes decreased with a median total loss of 21.3% and a median change rate of 0.7%/day. Parotids migrated toward the patient center with a median total distance change of 5.26 mm and a median change rate of 0.22 mm/day. A third study of 82 head and neck cancer patients showed an average volume loss in parotid glands of 20.0%, 26.9%, and 27.2% after 3 weeks mid-treatment, at treatment completion, and 2 months post-treatment, respectively [41]. These gland volume reductions correlated significantly with mean dose to the irradiated glands: volume loss with higher mean parotid doses (>30 Gy) to the glands was significantly greater than for lower mean parotid doses ($P<0.001$).

Finally, nearly all patients lose weight throughout their course of treatment. Barker et al. [6•] found that the median weight change from the start to completion of treatment was −7.1% (range, +5.2% to −13.0%) in their study. Reductions in external skin contours at the level of the C2 vertebral body and at the base of skull correlated with weight loss. Median weight loss correlated significantly with

median parotid medial displacement over time ($P<0.001$). This confirms that skin contours and weight loss can potentially be used as convenient surrogates for underlying anatomy changes.

Under the Hood: Technical Building Blocks for Adaptive Radiotherapy

The Current Standard—H&N Image-Guided Radiation Therapy (IGRT)

The term IGRT refers to the use of in-room imaging to make straightforward daily setup corrections, such as translational position shifts. IGRT does not involve modification of the original IMRT treatment plan. Thus, current IGRT techniques, while useful, only correct for the simplest of setup errors. In-room 2D stereoscopic imaging and 3D volumetric imaging are the most commonly used techniques for H&N IGRT.

IGRT workflow for H&N patients is not significantly different from other treatment sites, although an ROI must be identified as a reference point for daily treatment alignment. Previous studies have shown that the relative movement of different ROIs can be significant in the neck [32, 39]. Since spinal cord sparing is critical for most H&N cases, a vertebral body is generally a good reference ROI. Although a PTV may be used in some cases, use of GTV as an alignment target is not advisable since asymmetric tumor shrinkage can affect the relationship of GTV to isocenter and avoidance structures.

Beyond IGRT—The Workflow for Image-Guided Adaptive Radiotherapy

In contrast to simple image-guided setup for repositioning treatment fields, the intent of ART is to directly modify a radiation treatment plan to account for changes in anatomy. In theory, ART can occur at three different timescales: offline between daily treatment fractions; online immediately prior to a fraction; and in real-time during a treatment fraction. ART can be tightly linked to standard IGRT processes because any volumetric images acquired for IGRT could also be used for monitoring changes in anatomy and designing new plans.

Deformable Image Registration for Auto-Segmentation

Manual segmentation of treatment planning images demands too much physician and staff effort to be practical for routine use of ART in the community setting. Manual contouring would also be susceptible to intra-observer or inter-observer variations [42], which adversely affect the consistency of treatment quality. Deformable image registration for atlas-based auto-segmentation is an effective alternative for serial adaptive replanning [43–47]. Deformable image registration is a geometric mapping process that creates one-to-one correspondence between two images of the same object deformed across time. If the contours exist in one of the reference CT images, deformable transformation can be used to transform reference contours onto the newly acquired CT images with minimal manual input. This is well suited for ART, given that the original treatment plan can serve as the reference for this process.

An example of using deformable image registration for auto-segmentation is shown in Fig. 2. The process starts with a rigid alignment of bony structure (C2 vertebra) between the reference planning CT (left) and the daily in-room CT (middle and right). The necessary planning contours are overlaid onto the daily CT to verify setup accuracy and to ascertain whether significant anatomic changes have occurred at interval. If the changes are significant (for example, the original clinical target volumes no longer adequately cover gross disease visualized on daily CT images), deformable image registration can be performed to propagate the planning contours to the daily anatomy. The resultant contours are shown to the right. The entire transformation takes seconds, making it relevant to either online or offline IMRT replanning. Manual physician re-contouring typically takes several hours [13], which would not be practical for online ART and would strain practical application of offline ART.

Is it Worth the Effort? The Potential Dosimetric Benefits of H&N ART

With deformable image registration for dose accumulation, it is possible to evaluate uncorrected IMRT relative to standard IGRT or fully adapted treatment. O'Daniel et al. [48] studied the differences between planned and delivered parotid gland and target doses in a group of H&N cancer patients receiving standard IMRT. The clinical IMRT plans, designed with 3-mm to 4-mm PTV margin expansions, were recalculated on the repeat CT images. Deformable image registration software was used to map daily dose distributions to the original treatment plan and to calculate a cumulative delivered dose distribution. Without IGRT, dose to the parotid gland increased above the planned dose by 5–7 Gy in 45% of the patients. Use of IGRT aligned to the C2 vertebral body provided modest but significant parotid dose reductions in 91% of patients (median, 2 Gy). Nonetheless, the parotid dose from bone alignment remained greater than planned doses (median, 1.0 Gy, $P=0.007$) due to parotid shrinkage and movement. Lee et al. [49] also analyzed changes in parotid gland dose in ten patients via deformable image registration. They found that the daily parotid mean doses differed from the original plan by an average of 15%.

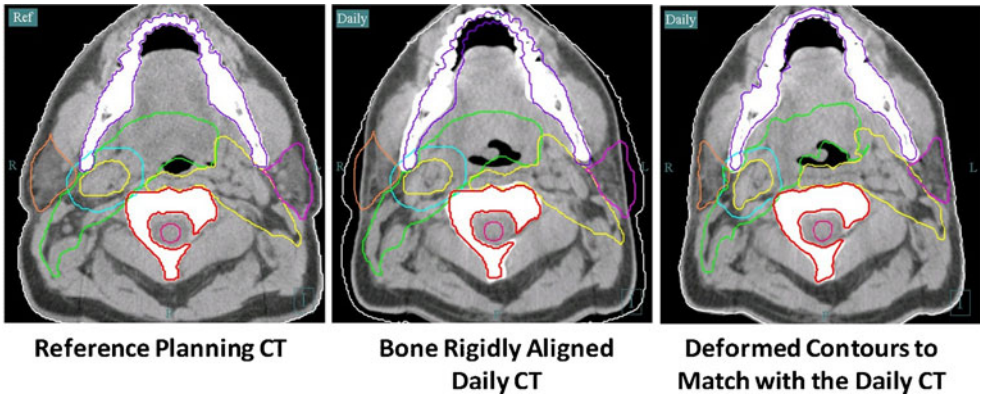

Fig. 2 The ART process starts with rigid alignment between the reference planning CT and the daily in-room CT (*left* and *middle*). The planning contours are overlaid to the daily CT to verify setup accuracy and to evaluate changes in anatomy relative to baseline. If changes are significant, as illustrated in the *middle* picture, a deformable image registration can be performed to propagate original planning contours onto current anatomy. Final deformed contours are shown on the *right*. (With permission from Elsevier.)

At the end of treatment, three of the ten patients were estimated to have received and unintended >10% increase in mean parotid dose (range, 13%–42%), correlating with medial drifting of the parotids toward high-dose target volumes.

Wu et al. [50••] performed a detailed H&N ART simulation study to evaluate the potential impact of different adaptive strategies. Eleven patients underwent six weekly helical CTs during routine IMRT. No PTV expansion margins were used for ART replanning. Significant increases in parotid dose were observed if ART was not used. The authors reported that one adaptive replanning during mid-course improves parotid mean dose sparing by 3%, two replannings by 5%, and six replannings by 6% if a 1-week delay is required between adaptive replanning and actual institution of ART delivery. If six weekly ART replans are immediately used for treatment, parotid dose sparing is improved by 8%. However, these calculations assumed that each new plan is executed without additional setup errors or non-rigid changes.

Early Clinical Experience with Automated H&N ART

Is automated H&N ART feasible, and what is its clinical impact? A prospective clinical trial led by the author at the University of Texas M.D. Anderson Cancer Center has been addressing these questions in oropharyngeal cancer patients. Patients with locally advanced AJCC stage III–IV disease have been eligible for inclusion. Baseline IMRT planning follows standard institutional guidelines, and in-room CT-guided IGRT is used for each treatment session, and the supervising physician evaluates each daily setup. If the physician notes significant anatomic changes resulting in geographical miss of gross tumor or inadequate sparing of normal tissues (particularly parotid glands or larynx), more comprehensive dosimetric evaluation is instigated. Deformable image registration is performed with a validated in-house version of Thirion's Demons algorithm [44] which is used to transfer the initial contours (GTV, CTV, parotid, spinal cord, larynx, and other normal structures) to the most recent in-room daily CT image set. Isocenter information and the original IMRT plan are then loaded into a new plan based on the newly acquired CT image set. Additional planning constraints may be added to improve the quality of the new plan for each individual case.

It is important to emphasize that our adaptive replanning approach does not employ geometric PTV expansions; PTVs remain identical to newly modified CTVs. Our pilot experience has confirmed precise set-up reproducibility with IGRT once patients have acclimated to treatment. Additional experience has confirmed that standard 3–4 mm PTV expansion margins are too generous to maintain parotid dose sparing [48]. Outside of the absence of PTV expansions, ART planning does not differ from standard IMRT planning. Therefore, the intent for ART is to recapitulate the treatment planning goals of the original IMRT plan as faithfully as possible, rather than to create novel planning guidelines.

An example of ART dose recalculation and replanning is shown in Fig. 3. On the left, the original plan is calculated onto current anatomy. Due to loss of weight and tissue separation, there is less attenuation of each IMRT beam. As a result, the original plan provides inappropriately large treatment margins and dose heterogeneity within the high-dose CTV. In the middle figure, a previous ART replan (ART1, designed at the 15th treatment fraction) is calculated onto current anatomy. The ART1 replan significantly improves dose conformality because PTV expansions are not used. On the right, a second ART replan (ART2) provides further improvement of contralateral parotid sparing and a lower scattered body dose relative to the ART1 plan.

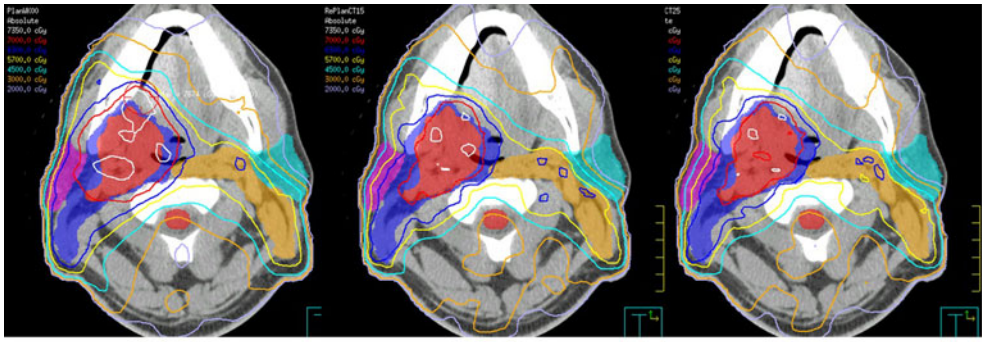

Fig. 3 An example of serial ART dose recalculation using a daily CT image acquired at the 25th treatment fraction. On the *left*, the original plan is calculated on current anatomy. The original plan provides inappropriate treatment margins and dose heterogeneity within the high-dose CTV. In the *middle* figure, an earlier ART replan (ART1, designed at the 15th treatment fraction) is calculated onto current anatomy. On the *right*, a second ART replan (ART2) is designed and calculated for the current daily image set. The ART2 plan provides improved contralateral parotid sparing and a lower total body dose than the ART1 plan. (With permission from Elsevier.)

A preliminary analysis of 724 daily CT images in the first 22 patients who completed a full course of ART for oropharyngeal cancer has been performed. The cohort was composed of 21 males and 1 female; median age was 55 (range: 42–75 years). Two patients had AJCC stage III disease and 20 patients had stage IVA disease, 19 of whom had N2 disease. Eight patients had T3–4 disease. Ten patients had a history of >10 pack-year cigarette smoking (range: 10–72); 2 of these patients (with 20 and 38 pack-yr exposures) had HPV-positive disease by both p16 immunohistochemistry and high-risk HPV in situ hybridization. Eleven patients were lifetime non-smokers and one patient had a 1.5 pack-yr exposure; 3 of these patients had HPV-positive disease.

Dosimetric Outcomes

All patients received at least one replan and eight patients (36%) received two replans during their course of treatment. As illustrated in Fig. 4, we compared three alternative planning scenarios: 1) the original IMRT plan aligned to the marked isocenter (BB); 2) the original plan aligned according to daily bone alignment (IGRT); and 3) IGRT with adaptive replanning (IGRT with either one [ART1] or two adaptive replans [ART2]). Initial ART replanning reduced the mean dose to contralateral parotid by 0.6 Gy or 2.8% (P=0.003) and ipsilateral parotid by 1.3 Gy (3.9%) (P=0.002) over the IGRT-only group. In patients who underwent a second ART replanning, ART2 further reduced the mean contralateral parotid dose by 0.8 Gy or 3.8% (P=0.026) and ipsilateral parotid dose by 4.1 Gy or 9% (P=0.001).

Two cases would have suffered from underdosing of high-risk CTV by >5% (range: −7.1% to −5.5%) because of daily setup errors if they had been treated with BB-alignment alone. In contrast, both IGRT and ART prevented underdosing to high-risk CTV in all cases, confirming both the clinical benefit of current IGRT and the safety of our PTV expansion strategy. Importantly, ART replanning also significantly reduced incidental whole body exposure to 40 Gy and 60 Gy relative to IGRT alone, although this reduction in integral bystander tissue dose was not preserved for lower dose levels.

Disease Outcomes

With a median follow-up of 30 months (range: 12–44), there has been one nodal relapse, yielding an estimated 100% local and 95% regional disease control rate at 2 years. The single case of neck failure was surgically salvaged and remains free of disease. Eight additional patients underwent consolidative neck dissection surgery for persistent adenopathy; none of these patients had residual viable disease in their surgical specimens. No distant disease relapses or deaths have occurred.

Toxicity

Acute toxicity manifested predominantly as radiation mucositis, dermatitis, and xerostomia (9 patients grade 1; 12 patients grade 2; 1 patient grade 3). Eighteen (82%) required gastrostomy tube (PEG) placement for nutritional support; these tubes were ultimately removed in all cases. Quality-of-life instruments have demonstrated functional recovery of speech and eating function domains by 20 months. Formal sialometry findings have confirmed ongoing recovery of stimulated salivary production after 1-year follow-up despite persistent loss of unstimulated salivary production, consistent with our institutional policy to prioritize parotid gland sparing at the cost of no formal sparing of submandibular glands. No patient

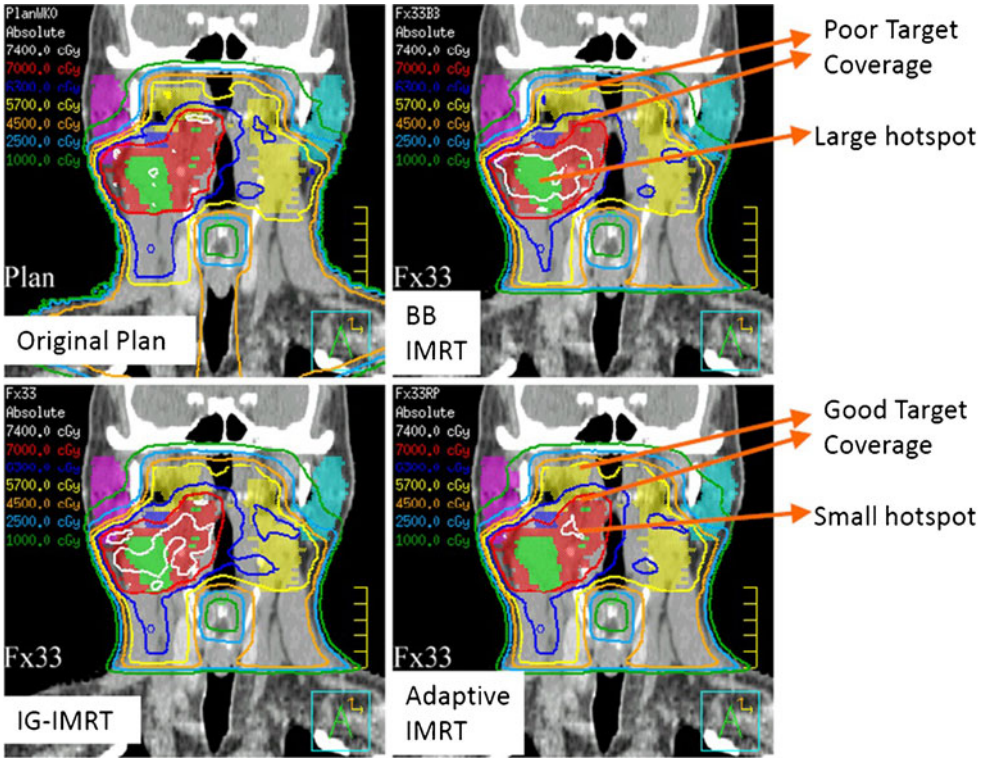

Fig. 4 An example of cumulative dose evaluation for IMRT treatments without daily image guidance (alignment to the surface markers or "BBs" on the immobilization device) (BB-IMRT), image-guided IMRT (IG-IMRT), and image-guided adaptive IMRT (adaptive IMRT). In this case, BB-aligned IMRT was compromised by incomplete high-risk target coverage. Without adaptive modification, both BB-IMRT and IG-IMRT yielded hotter, more heterogeneous target volume coverage relative to the adaptive IMRT planning

demonstrated aspiration after 12 months by formal speech pathology assessment.

In summary, this trial is the first prospective demonstration of the feasibility of automated adaptive head and neck radiotherapy. Initial results suggest that conventional IGRT alone does not provide meaningful dosimetric benefit if conventional PTV margins are used. One properly timed adaptive replan appears to provide the majority of clinically relevant dosimetric improvements that are attainable through ART.

Future Directions for ART

Online Versus Offline Adaptive Radiotherapy

Online ART adjusts the treatment plan daily in real time using images acquired during each treatment session. An offline approach, on the other hand, uses imaging information from a previous time point for planning changes incorporated into a later treatment fraction. The online approach can potentially provide greater treatment precision, albeit at a cost of increased daily effort and treatment time. Online ART is challenging due to uncompromising time constraints (the patient remains immobilized on the treatment couch while waiting for ART corrections). For H&N radiation treatment, most anatomic changes take place gradually over the first few weeks of therapy. There is no pressing need for real-time intervention unless an unforeseen event occurs, such as acute development of edema or disease progression. Therefore, offline adaptive radiotherapy is a more practical approach for the vast majority of H&N cases, which should facilitate adoption of ART into routine clinical practice.

Correction for Non-Rigid Setup Error

In H&N radiotherapy patients, it is common for spinal anatomy to exhibit complex geometric changes. If these non-rigid changes are systematic (ie, caused by impropriate simulation procedures), adaptive replanning can be used to correct these non-rigid systematic setup errors even if tumor target volumes have not changed. Our experience showed that random non-rigid setup errors are difficult to correct. Repositioning the patient usually does not fully correct these errors. In special cases (ie, retreatment of areas close to critical structures, such as central nervous tissues) where desired accuracy requires daily real time correction of random (non-rigid) setup error, then online ART may become desirable.

Auto-Replanning

IMRT replanning remains a time-consuming process. For ART to become broadly accepted and used, it will be critical to reduce its resource requirements through effective automated planning techniques. Although replanning benefits

from baseline information provided by original IMRT plan, manual trial-and-error currently remains necessary to fine-tune planning parameters for optimization. Several groups have studied auto-replanning algorithms. In almost all cases, deformable image registration is a critical component of this process. Mohan et al. [9] used an IMRT intensity warping technique to adapt an IMRT plan based on the changes in the anatomy in the beam's-eye-view projection. This study provided proof-of-principle that auto-planning is feasible and can approximate the quality of manual treatment planning. However, a deformed intensity map may not always be clinically deliverable. To reduce the likelihood for such a possibility, Ahunbay et al. [51] proposed a more sophisticated two-step procedure for auto-replanning. The first step uses an aperture morphing technique to transform MLC leaf segment based on anatomy changes. The second step applies a segment weight optimization, which re-optimizes the entire plan. The entire process takes 5–8 min, confirming the real-world feasibility of such an approach. Continued improvement of auto-replanning, therefore, promises to make routine online adaptive radiotherapy a possibility. It may also reduce manual workload requirements for offline ART as well.

Adaptive Dose Painting by Numbers

"Dose painting by numbers" is a descriptive moniker for a novel, intellectually appealing approach to treatment planning entailing delivery of non-homogenous dose based both on morphologic and biological data acquired by advanced functional imaging. In theory, this approach directly informs and tailors IMRT planning to compensate for heterogenous tumor biology (ie, more or less treatment-resistant tumor subregions) and/or at-risk bystander structures (such as salivary glands or central nervous system structures) detected and localized by functional imaging techniques. This strategy could potentially apply to any relevant molecular or vascular imaging approach; currently available examples of such imaging include positron emission tomography (PET), single-photon emission computed tomography (SPECT), and dynamic contrast-enhanced or diffusion-weighted MRI techniques. Recent pilot clinical trials have supported the feasibility of FDG-PET–guided radiation dose boosting to metabolically active tumor subvolumes [52, 53] and [^{18}F]-fluoromisonidazole (FMISO)-PET guided dose escalation to potentially radiation-resistant hypoxic tumor subvolumes [54] in patients with locally advanced H&N disease. Additional work has suggested that serial acquisition of multi-modality PET/MRI functional imaging can feasibly guide adaptive H&N dose painting [55•]. These remain early days in the formulation of this very complex approach. Formal prospective trial testing must be pursued to confirm that the theoretical benefits of adaptive dose painting as a "next step" beyond standard IMRT or anatomic-imaging guided ART are matched by real-world outcome improvements.

Conclusions

In the clinic, IMRT replanning strategies remain difficult and time consuming. Early preclinical and clinical trial work employing automated deformable image registration has demonstrated the feasibility and dosimetric advantages of head and neck ART. As ART outcomes mature and incorporation of volumetric imaging into ART becomes increasingly sophisticated, we expect ART to evolve into a routine component of H&N radiation treatment. Nonetheless, the optimal frequency and utilization, as well as the ultimate clinical impact of ART remain undefined, and prospective clinical trials will be necessary to appropriately guide the maturation of ART into an accepted treatment standard.

Disclosure No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Sobel S, Rubin P, Keller B, Poulter C. Tumor persistence as a predictor of outcome after radiation therapy of head and neck cancers. Int J Radiat Oncol Biol Phys. 1976;1(9–10):873–80.
2. Barkley HT, Fletcher GH. The significance of residual disease after external irradiation of squamous-cell carcinoma of the oropharynx. Radiology. 1977;124(2):493–5.
3. Suit HD, Walker AM. Assessment of the response of tumours to radiation: clinical and experimental studies. Br J Cancer Suppl. 1980;41 Suppl 4:1–10.
4. Trott KR. Human tumour radiobiology: clinical data. Strahlentherapie. 1983;159(7):393–7.
5. Bhide SA, Davies M, Burke K, et al. Weekly volume and dosimetric changes during chemoradiotherapy with intensity-modulated radiation therapy for head and neck cancer: a prospective observational study. Int J Radiat Oncol Biol Phys. 2010;76(5):1360–8.
6. • Barker JL, Jr., Garden AS, Ang KK, et al. Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system. Int J Radiat Oncol Biol Phys. 2004;59(4):960–70. *A seminal study utilizing serial in-room CT imaging to catalog volumetric and positional tissue changes occurring during a course of H&N IMRT treatment, particularly changes involving parotid glands and tumor volumes.*

7. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol. 2011;12(2):127–36.
8. Hansen EK, Bucci MK, Quivey JM, et al. Repeat CT imaging and replanning during the course of IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2006;64(2):355–62.
9. Mohan R, Zhang X, Wang C, et al. Deforming intensity distributions to incorporate inter-fraction anatomic variations for image-guided IMRT. Int J Radiat Oncol Biol Phys. 2004;60(1): S226–S7.
10. Court LE, Dong L, Lee AK, et al. An automatic CT-guided adaptive radiation therapy technique by online modification of multileaf collimator leaf positions for prostate cancer. Int J Radiat Oncol Biol Phys. 2005;62(1):154–63.
11. Court LE, Tishler RB, Petit J, et al. Automatic online adaptive radiation therapy techniques for targets with significant shape change: a feasibility study. Phys Med Biol. 2006;51(10):2493–501.
12. Gregoire V, Levendag P, Ang KK, et al. CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines. Radiother Oncol. 2003;69(3):227–36.
13. Chao KSC, Bhide S, Chen H, et al. Reduce in variation and improve efficiency of target volume delineation by a computer-assisted system using a deformable image registration approach. Int J Radiat Oncol Biol Phys. 2007;68(5):1512–21.
14. Gregoire V, De Neve W, Eisbruch A, et al. Intensity-modulated radiation therapy for head and neck carcinoma. Oncologist. 2007;12(5):555–64.
15. Eisbruch A, Gregoire V. Balancing risk and reward in target delineation for highly conformal radiotherapy in head and neck cancer. Semin Radiat Oncol. 2009;19(1):43–52.
16. Nangia S, Chufal KS, Tyagi A, et al. Selective nodal irradiation for head and neck cancer using intensity-modulated radiotherapy: application of RTOG consensus guidelines in routine clinical practice. Int J Radiat Oncol Biol Phys. 2009.
17. Eisbruch A, Ten Haken RK, Kim HM, et al. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys. 1999;45(3):577–87.
18. Chao KS, Deasy JO, Markman J, et al. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results. Int J Radiat Oncol Biol Phys. 2001;49(4):907–16.
19. Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys. 2007;68(5):1289–98.
20. Schwartz DL, Hutcheson K, Barringer D, et al. Candidate dosimetric predictors of long-term swallowing dysfunction after oropharyngeal intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys. 2010;78(5):1356–65.
21. Chao KS, Majhail N, Huang CJ, et al. Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control in patients with oropharyngeal carcinoma: a comparison with conventional techniques. Radiother Oncol. 2001;61 (3):275–80.
22. Lee N, Xia P, Quivey JM, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. Int J Radiat Oncol Biol Phys. 2002;53(1):12–22.
23. Eisbruch A, Rhodus N, Rosenthal D, et al. The prevention and treatment of radiotherapy-induced xerostomia. Semin Radiat Oncol. 2003;13(3):302–8.
24. Hong TS, Tome WA, Chappell RJ, et al. The impact of daily setup variations on head-and-neck intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys. 2005;61(3):779–88.
25. Prisciandaro JI, Frechette CM, Herman MG, et al. A methodology to determine margins by EPID measurements of patient setup variation and motion as applied to immobilization devices. Med Phys. 2004;31(11):2978–88.
26. Gregoire V, Daisne JF, Geets X, Levendag P. Selection and delineation of target volumes in head and neck tumors: beyond ICRU definition. Rays. 2003;28(3):217–24.
27. Manning MA, Wu Q, Cardinale RM, et al. The effect of setup uncertainty on normal tissue sparing with IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2001;51(5):1400–9.
28. Hatherly KE, Smylie JC, Rodger A, et al. A double exposed portal image comparison between electronic portal imaging hard copies and port films in radiation therapy treatment setup confirmation to determine its clinical application in a radiotherapy center. Int J Radiat Oncol Biol Phys. 2001;49(1):191–8.
29. Bel A, Keus R, Vijlbrief RE, Lebesque JV. Setup deviations in wedged pair irradiation of parotid gland and tonsillar tumors, measured with an electronic portal imaging device. Radiother Oncol. 1995;37(2):153–9.
30. Willner J, Hadinger U, Neumann M, et al. Three dimensional variability in patient positioning using bite block immobilization in 3D-conformal radiation treatment for ENT-tumors. Radiother Oncol. 1997;43(3):315–21.
31. Karger CP, Jakel O, Debus J, et al. Three-dimensional accuracy and interfractional reproducibility of patient fixation and positioning using a stereotactic head mask system. Int J Radiat Oncol Biol Phys. 2001;49(5):1493–504.
32. Li H, Zhu XR, Zhang L, et al. Comparison of 2D radiographic images and 3D cone beam computed tomography for positioning head-and-neck radiotherapy patients. Int J Radiat Oncol Biol Phys. 2008;71(3):916–25.
33. Court L, Rosen I, Mohan R, Dong L. Evaluation of mechanical precision and alignment uncertainties for an integrated CT/LINAC system. Med Phys. 2003;30(6):1198–210.
34. Jaffray DA, Drake DG, Moreau M, et al. A radiographic and tomographic imaging system integrated into a medical linear accelerator for localization of bone and soft-tissue targets. Int J Radiat Oncol Biol Phys. 1999;45(3):773–89.
35. Kuriyama K, Onishi H, Sano N, et al. A new irradiation unit constructed of self-moving gantry-CT and linac. Int J Radiat Oncol Biol Phys. 2003;55(2):428–35.
36. Mackie TR, Kapatoes J, Ruchala K, et al. Image guidance for precise conformal radiotherapy. Int J Radiat Oncol Biol Phys. 2003;56(1):89–105.
37. Ahn PH, Ahn AI, Lee CJ, et al. Random positional variation among the skull, mandible, and cervical spine with treatment progression during head-and-neck radiotherapy. Int J Radiat Oncol Biol Phys. 2009;73(2):626–33.
38. Zhang L, Garden AS, Lo J, et al. Multiple regions-of-interest analysis of setup uncertainties for head-and-neck cancer radiotherapy. Int J Radiat Oncol Biol Phys. 2006;64(5):1559–69.
39. van Kranen S, van Beek S, Rasch C, et al. Setup uncertainties of anatomical sub-regions in head-and-neck cancer patients after off-line CBCT guidance. Int J Radiat Oncol Biol Phys. 2009;73(5):1566–73.
40. Lee C, Langen KM, Lu W, et al. Evaluation of geometric changes of parotid glands during head and neck cancer radiotherapy using daily MVCT and automatic deformable registration. Radiother Oncol. 2008;89(1):81–8.
41. Wang ZH, Yan C, Zhang ZY, et al. Radiation-induced volume changes in parotid and submandibular glands in patients with head and neck cancer receiving postoperative radiotherapy: a longitudinal study. Laryngoscope. 2009;119(10):1966–74.

42. Geets X, Daisne JF, Arcangeli S, et al. Inter-observer variability in the delineation of pharyngo-laryngeal tumor, parotid glands and cervical spinal cord: comparison between CT-scan and MRI. Radiother Oncol. 2005;77(1):25–31.
43. Lu W, Chen ML, Olivera GH, et al. Fast free-form deformable registration via calculus of variations. Phys Med Biol. 2004;49 (14):3067–87.
44. Wang H, Dong L, O'Daniel J, et al. Validation of an accelerated 'demons' algorithm for deformable image registration in radiation therapy. Phys Med Biol. 2005;50(12):2887–905.
45. Castadot P, Lee JA, Parraga A, et al. Comparison of 12 deformable registration strategies in adaptive radiation therapy for the treatment of head and neck tumors. Radiother Oncol. 2008;89(1):1–12.
46. Zhang T, Chi Y, Meldolesi E, Yan D. Automatic delineation of on-line head-and-neck computed tomography images: toward on-line adaptive radiotherapy. Int J Radiat Oncol Biol Phys. 2007;68 (2):522–30.
47. Nithiananthan S, Brock KK, Daly MJ, et al. Demons deformable registration for CBCT-guided procedures in the head and neck: convergence and accuracy. Med Phys. 2009;36(10):4755–64.
48. O'Daniel JC, Garden AS, Schwartz DL, et al. Parotid gland dose in intensity-modulated radiotherapy for head and neck cancer: is what you plan what you get? Int J Radiat Oncol Biol Phys. 2007;69 (4):1290–6.
49. Lee C, Langen KM, Lu W, et al. Assessment of parotid gland dose changes during head and neck cancer radiotherapy using daily megavoltage computed tomography and deformable image registration. Int J Radiat Oncol Biol Phys. 2008;71(5):1563–71.
50. •• Wu Q, Chi Y, Chen PY, et al. Adaptive replanning strategies accounting for shrinkage in head and neck IMRT. Int J Radiat Oncol Biol Phys. 2009;75(3):924–32. *This is among the most thorough preclinical H&N ART studies yet published. The authors comprehensively catalog and compare the potential impact of different clinically relevant adaptive strategies, including the potential dosimetric effects of alternative frequency and timing of ART replanning events.*
51. Ahunbay EE, Peng C, Godley A, et al. An on-line replanning method for head and neck adaptive radiotherapy. Med Phys. 2009;36 (10):4776–90.
52. Madani I, Duthoy W, Derie C, et al. Positron emission tomography-guided, focal-dose escalation using intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2007;68(1):126–35.
53. Vanderstraeten B, Duthoy W, De Gersem W, et al. [18F]fluoro-deoxy-glucose positron emission tomography ([18F]FDG-PET) voxel intensity-based intensity-modulated radiation therapy (IMRT) for head and neck cancer. Radiother Oncol. 2006;79 (3):249–58.
54. Lee N, Nehmeh S, Schoder H, et al. Prospective trial incorporating pre-/mid-treatment [18F]-misonidazole positron emission tomography for head-and-neck cancer patients undergoing concurrent chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2009;75 (1):101–8.
55. • Dirix P, Vandecaveye V, De Keyzer F, et al. Dose painting in radiotherapy for head and neck squamous cell carcinoma: value of repeated functional imaging with (18)F-FDG PET, (18)F-fluoromisonidazole PET, diffusion-weighted MRI, and dynamic contrast-enhanced MRI. J Nucl Med. 2009;50(7):1020–7. *This report shares results from an exciting proof-of-concept trial employing "brute force" multimodality functional imaging for biologically informed dose painting by numbers. Although this degree of image-based characterization is currently not feasible outside of experienced research centers, the manuscript provides potential insight into the future of image-guided H&N ART.*