Adaptive Radiation Therapy

Technical Components and Clinical Applications

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Abstract: In current standard radiation therapy process, patient anatomy is represented by the snapshot of computed tomographic images at the simulation for treatment planning. However, patient anatomy during the treatment course is not static, and the changes can be in the order of centimeters. The goal of the adaptive radiation therapy (ART) is to measure and account these variations in the treatment process, so that the optimal planned dose distribution is the same as the final delivered dose distribution. The field of the ART is rapidly evolving. The implementation of the ART principle is built on technical components in 3 main areas: image guidance, dose verification, and plan adaptation. The purpose of this review was to present different ART methods currently developed and used by different investigators.

Key Words: Adaptive, IMRT, optimization, replanning, reoptimization, image guidance

(*Cancer J* 2011;17: 182–189)

THE RATIONALE OF ADAPTIVE RADIATION THERAPY

External beam radiation therapy (EBRT) is the most commonly used technique in cancer radiotherapy. In EBRT, the radiation is delivered to the tumor region, that is, target volume, from outside the patient's body by using several radiation beams from different directions. This configuration is similar to the "cross-firing" concept because all radiation beams are focused on the target. Thus, the radiation dose from all beams accumulates inside the body to form a three-dimensional dose distribution, with high dose only covering the entire target volume and reduced dose to the surrounding normal tissues/organs, that is, organs-at-risk (OARs). The latest technology, intensity-modulated radiation therapy (IMRT), further improves the OAR sparing via nonuniform beam delivery. An example of IMRT is shown in Figure 1.

Such radiation treatment (RT) design is based on the three-dimensional volumetric imaging such as computed tomography (CT) and magnet resonance imaging (MRI) to capture the anatomic information about the patient and geometrical relationships of the tumor and OARs and the functional and molecular imaging such as positron emission tomography (PET) and single photon emission CT to capture features about the tumor's extent and staging. The team of radiation oncologist, physicist, and dosimetrist works together to design an individualized treatment plan for each patient. This treatment plan is designed once and delivered during a course of 30 to 40 daily treatment sessions.

During the actual daily treatment, the radiation is delivered according to the treatment plan by assuming that the daily anatomy remains the same as in the initial planning stage. In reality, this assumption may not always be valid because of the daily change in the anatomy, the target shape, and the position, in particular, and may therefore lead to mismatch between delivered dose distribution and the "anatomy-of-the-day" scenario. Such mismatch could result in underdosing the target and/or overdosing the healthy tissues/organs, which may translate into compromised tumor control and/or increased adverse effects.

In general clinical practice, the risk of underdosing daily target is addressed by adding a margin around the true target during treatment planning[1] and designing the dose distribution to conform to the expanded target, termed as *planning target volume* (PTV). This technique leaves some "headroom" for anatomy variations and patient setup errors, but at the cost of increasing dose to the surrounding normal tissue/organs. The IMRT significantly reduces the excessive dose outside the target by providing more conformal dose distribution to the target. Thus, the concern of underdosing target due to anatomy change is of greater importance with IMRT because a higher dose gradient means less tolerance and, consequently, higher probability of inadequate daily target coverage.

The adaptive radiation therapy (ART) approaches this issue by changing the fundamental assumption of *stationary anatomy* in traditional EBRT to *variable anatomy* and integrating this concept through the entire treatment course. The principle of ART is to capture the anatomic change, to modify the treatment plan accordingly, and to ensure the optimal target coverage and OAR sparing in both planning and daily treatment.

COMPONENTS OF ART

The implementation of the ART principle is built on technical components in 3 main areas: image guidance, dose verification, and plan adaptation (Fig. 2).

Image Guidance

Adaptive radiation therapy is the advanced stage of image-guided radiation therapy (IGRT). The role of imaging has become increasingly important in nearly every aspect of radiation therapy, from staging, structure contouring, treatment planning, treatment delivery verification, to treatment response and assessment.[2] In the field of ART, image guidance provides the input information of daily anatomy, enables the visualization of the anatomy-of-the-day, and determines how different the anatomy is from the plan. Image guidance in ART commonly includes 2 steps: volumetric image acquisition and image registration.

Daily Anatomic Image Acquisition

Daily image acquisition techniques for ART have been reported by various groups. Court et al[3–7] reported using CT-on-rails as an in-room daily image acquisition technique for ART. By installing a diagnostic quality helical CT scanner that shares the couch with the LINAC on-rails in the treatment room, high-quality CT image can be obtained before treatment while keeping patients in the same relative position to the treatment couch. Soon after that, the cone beam CT (CBCT) system integrated to the

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ISSN: 1528-9117

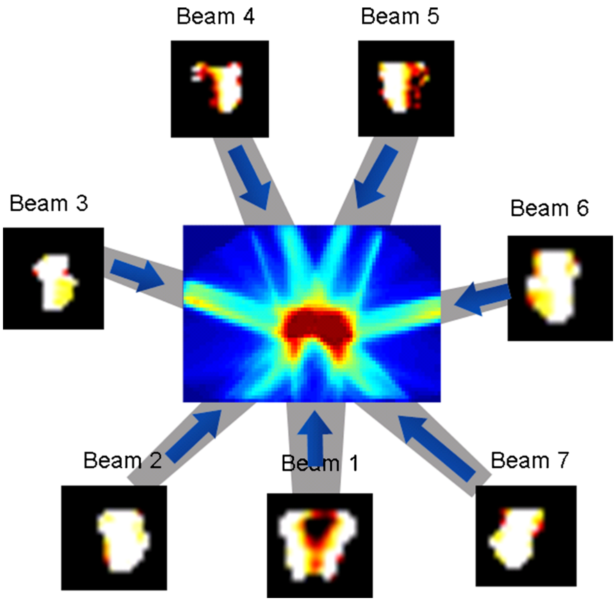

FIGURE 1. Demonstration of IMRT. In this example, 7 beams with different shape and nonuniform intensity converges at the target area. The two-dimensional intensity-modulated photon fluence accumulates to provide a conformal dose distribution around the target region, as the color wash indicating the dose range from high to low.

gantry of the medical linear accelerator (LINAC) has also been reported as a component in ART.[8–11] The CBCT for ART enables the patient to be imaged and treated at the same position, which minimizes the uncertainty associated with the imaging procedure. Integrated CBCT eliminates the need to rotate the patient and move the CT scanner between imaging and treatment and is therefore more convenient. However, the image quality of the current CBCT is generally inferior to that of helical CT in soft tissue contrast, CT number consistency, and artifacts. Alternatively, the megavoltage (MV) CT capability of the Tomotherapy (TomoTherapy, Inc, Madison, WI) treatment unit has also been reported for daily image acquisition and target localization.[12] The Tomotherapy unit uses the same MV x-ray source mounted in a CT-like gantry for treatment and imaging. It rotates helically around the patient to perform both the imaging and the therapy process.[13]

Image Registration

Image registration is a tool used to determine the difference between planning anatomy and the daily anatomy. It can be categorized into 2 groups: rigid registration and nonrigid/deformable registration.

Rigid registration matches the daily images to the reference images such as planning CT via three-dimensional translational or three-dimensional translational + three-dimensional rotational transformation, which can then be used to reposition the patient for target alignment. The rigid registration technique offers fast and robust performance in daily-to-planning target alignment and is therefore currently widely adopted in the clinical practice of IGRT. However, at the presence of target/organ deformation or tumor shrinkage, rigid registration may not be sufficient to provide the information on the shape and volume variations.[8]

Deformable registration techniques, on the other hand, allow the voxel-to-voxel mapping between the daily and the planning image sets. Yan et al[14] reported a deformable registration method using biomechanical model of elastic body and demonstrated a framework to construct the cumulative dose distribution in organs during the course of radiation therapy. Coselmon et al[15] developed mutual information–based CT registration method using thin-plate splines for lung deformation with alignment accuracies of 1.7, 3.1, and 3.6 mm in right-to-left, anterior-posterior, and inferior-superior directions. The study of Wang et al[16] on an accelerated "demons" algorithm showed approximately 1.5 pixels of registration error in simulated CT images and in pelvis phantom cases and acceptable contour-propagation accuracy in patient study. Lu et al[17] demonstrated the feasibility using free-form deformation method between kilovolt and MV CT images in ART for "automatic recontouring, deformable dose accumulation and tumor volume monitoring." They have also cautioned that,

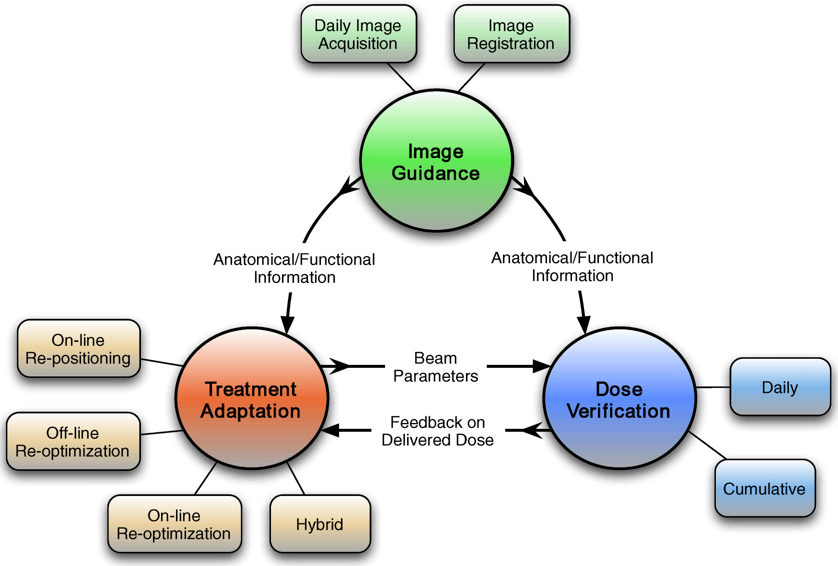

FIGURE 2. Components of the ART system.

"under circumstances where large topological changes present, the intensity-based deformable registration technique may fail." In a multi-institutional phantom study of several deformable registration algorithms, Kashani et al[18] found that large registration errors exist at various phantom regions for different techniques compared and suggested that deformable registration techniques should be used cautiously. They observed that, for the same type of registration, "different implementations, different users, or different parameter settings," for example, imaging modalities, image quality, registration site, can significantly alter the registration result and its accuracy. Therefore, before clinical use, any deformable registration technique should be carefully validated within the context of the specific implementation, the clinical environment (modalities, image quality, sites), and user-defined parameters.

Functional Imaging

As the field of radiation oncology progresses to include more biologic and functional information into the patient care process, functional imaging modalities, for example, dynamic contrast-enhanced MRI (DCE-MRI) and PET, have attracted increasing interests. Some pilot studies have demonstrated unique perspectives and promising results of these imaging modalities in guiding radiation therapy. Cao et al[19] reported using DCE-MRI to assess factors influencing the clinical outcome of high-grade gliomas after radiation therapy and found that both vascularity and tumor volume influences the time to progression for these patients. Craciunescu et al[20] piloted a study using DCE-MRI to predict the treatment response in patients with breast cancer. Mayr et al[21] reported a study using DCE-MRI to correlate the tumor perfusion pattern change (before RT, during early RT, and mid-RT) and the treatment outcome. The results indicated that DCE-MRI can be used in monitoring tumor radioresponsiveness during RT for guiding adaptive therapy. Magnetic resonance imaging guidance is also reported by Dimopoulos et al[22] for being effective in assessing the tumor volume shrinkage during EBRT and brachytherapy for cervical cancer. Schuetz et al[23] evaluated repetitive ^{18}F-fluoroazomycin-arabinoside (^{18}FAZA) PET scans to map tumor hypoxia during EBRT and MRI-guided brachytherapy for cervical cancer and found it feasible but has questionable clinical value in addition to MRI. Fallone et al[24] reported first on-board MR images acquired concurrently with EBRT with in-house developed MR-LINAC featuring 0.2-T field strength. The acceptable image quality shows promises of using MR over CT/CBCT in adaptive radiotherapy for better soft tissue contrast. Geets et al[25] used FDG-PET to monitor tumor volume change during RT treatment, parallel to CT and MRI, and performed adaptive replanning study based on target delineated from PET, CT, and MRI. They found that gross tumor volumes (GTVs) delineated with functional imaging modality were always smaller compared with using anatomic imaging; adaptive replanning, coupled with target delineated from repeated FDG-PET, has resulted in a 15% to 40% reduction on the irradiated volumes (V90, V95, and V100) compared with pretreatment CT. For online target localization, Roper et al[26] reported a simulation study exploring the feasibility of an on-board single photon emission CT and found it valuable in localizing less than 2-cm tumors with clinical uptake of technetium-99 m in 4 minutes of scan time.

The use of functional imaging modality in ART is still in the early stage with many technical challenges and limited research data. Although the additional biologic information is promising in principle, more systematic studies are needed to justify the added benefit of functional imaging to current anatomic imaging modalities and then to facilitate the clinical implementation of these technologies.

Treatment Adaptation

The treatment adaptation is another major component of ART; it takes the information from the image guidance as input and mitigates the discrepancies between planned and actual anatomy, aiming for optimal target coverage and OAR sparing. With this goal in mind, several methods and protocols have been developed in research, some of which have already been implemented clinically. These methods can be categorized into 4 groups:

Online Repositioning

Online repositioning is the first stage of ART and has been widely implemented in clinics where IGRT technology is available. The patient's position is corrected online using daily images for possible target position change from the planned anatomy. Different landmarks can be used to drive the realignment of the target volume. Most commercial treatment delivery systems offer the online registration of bony structures for patient positioning correction, which is useful when tumor location is relatively stable in reference to the body structures, for example, intracranial tumors, but not sufficient for treatment sites such as lung and abdomen. To improve the target localization, fiducial markers implanted in the soft tissue have been used as surrogates for the target. Chung et al[27] evaluated using fiducial markers in performing online target localization and alignment for prostate cancer treatment, which is widely implemented in clinical practice. Jaffray et al[11] demonstrated using CBCT with soft tissue matching to reduce interfractional target position uncertainties. This method is also widely implemented in commercial treatment delivery systems and is used clinically. Barney et al[28] compared CBCT-based IGRT with fiducial marker–based prostate cancer treatment and found them to be similar, although fiducial marker–based technique is preferred for efficiency. Wu et al[29] performed geometric and dosimetric evaluations of online repositioning and demonstrated its effectiveness on reducing the CTV-PTV margin. Shi et al[30] compared manual fiducial marker alignment with automatic soft tissue match and found the latter less reliable for daily target alignment.

Although efficient and widely implemented, online repositioning alone is not capable of correcting dosimetric deficits resulted from daily target/organ deformation, which is commonly seen in prostate and head-and-neck cancer patients. Such changes require the plan to be modified through reoptimization-based techniques.

Offline Replanning

Yan et al[31] pioneered the study of ART by introducing offline reoptimization based on the bounding target volume constructed from the first several fractions of image data. After the first week's treatment, the plan can be reoptimized with the bounding target volume and used for subsequent fractions to improve the efficacy of the delivery.[32] Wu et al[33] demonstrated the feasibility of combining offline reoptimization and dose compensation to safely reduce the CTV-PTV margin. Similar offline reoptimization has also been developed and evaluated by other groups of researchers.[10,34–38] Offline reoptimization for dose compensation has also been applied with the Tomotherapy unit.[39–41] Wu et al[40] proposed using offline reoptimization to compensate cold spots in target volume in the next fraction and demonstrated its effectiveness with simulated cases. Welsh et al[41] demonstrated the clinical implementation concept of compensating underdosed region in the target using dose comparison and Tomotherapy treatment technique in subsequent fractions. Woodford et al[42] investigated an adaptive radiotherapy planning technique based on daily GTV changes acquired in daily MV CT image and found it beneficial to perform adaptive planning for the subsequent fractions if GTV decreases by more than 30% during the treatment course. Nijkamp et al[37] at The Netherlands Cancer Institute reported their first clinical results on adaptive prostate radiotherapy. They performed offline reoptimization based on averaged PTV derived from the CBCT data in the first 6 fractions and found using this plan for the subsequent fractions to be effective in reducing high-dose regions and the dose to the rectum. One important notion of the offline optimization techniques is that the reoptimized plan is used for further treatments not for the current fraction when the daily image was acquired.

Online Adaptation

Because the ultimate goal of ART is to address the daily anatomy change, it is intuitive to develop optimization techniques that can be used online based on daily anatomic structures, *before the treatment*. Court et al[5,6] developed a technique of modifying multileaf collimator (MLC) positions that combines global rigid registration and slice-by-slice two-dimensional registration between planning and daily CT images to account for global shifts and regional deformation of the target, respectively. They found this technique to be effective in improving target dose uniformity for prostate and head-and-neck cases. Song et al[43] also reported the dosimetric evaluation on online correction method based on "monitor unit-MLC" modification. Mohan et al[44] reported online reoptimization by deforming two-dimensional intensity maps according to the geometric relationship between the intensity maps and projected anatomy in beams-eye-view and found it to be able to provide good approximation to the full-fledged replanning in a rapid manor. Fu et al[45] developed online MLC position modification techniques based on beams-eye-view anatomic structure projections with dosimetric benefits and faster speed. Feng et al[46] reported an effective and fast online plan adaptation method using direct aperture deformation that morphs the treatment apertures according to the planning-to-daily deformable registration. Wu et al[8] developed and evaluated a full volumetric online reoptimization algorithm using deformed planning dose distribution and linear programming optimization of the intensity maps, which significantly improves the target coverage and OAR sparing with less than 2 minutes of optimization time.[47] Ahunbay et al[48] used a 2-step optimization process called "SAM + SWO" as clinically implementable online reoptimization techniques. In this model, the MLC shape and its relevant monitor unit were optimized separately, which took a total of 5 to 10 minutes for plan adaptation. New development in graphics processing unit (GPU)-accelerated computing enables to perform full direct aperture optimization within 4 seconds, as demonstrated by Men et al.[49]

Hybrid Strategies of Plan Adaptation

Although reoptimization features the optimal target coverage and OAR sparing for a given daily anatomy, both online and offline implementations of such technique involve complicated procedures that add considerable extra resources burden to the clinic. In the meantime, online repositioning is still the simplest and most widely implemented correction technique for daily anatomic variations. For rigid target variations or small deformation, online repositioning remains a very effective and efficient method for treatment. However, for cases with significant target deformation, reoptimization based on the new anatomy is optimal for complete target coverage and ensuring OAR sparing. Therefore, combining online repositioning and offline/online reoptimization will likely maximize the benefit from both techniques and reduce redundant reoptimizations. Lei et al[9] reported that using offline reoptimization in conjunction with online repositioning correction is necessary and yields further margin reductions of 1.4 and 2.0 mm for low-risk and intermediate-risk prostate cancer patients, respectively, while maintaining a 99% target volume coverage. Li et al[50,51] designed and evaluated an ART strategy to combine online repositioning with online reoptimization and to expand the repositioning match to all delivered plans, that is, both original and reoptimized. A retrospective study of 18 patients with 10-fraction treatment courses demonstrated that this strategy is capable of offering consistent target coverage (CTV D99 >98% prescription dose for all 180 fractions) similar to daily replanning. Sparing of OAR is improved compared with current repositioning IGRT. Reusing previously delivered plans enabled a reduction of redundant reoptimizations during treatment by an average of 43%, improving the overall efficiency of online ART.

Dose Verification

Both Yan et al[31,52] and de la Zerda et al[10] formulated the ART process as a closed-loop system, where dose verification acts as a feedback chain to provide information on the dosimetric fidelity of the fractionated treatment process. The dose verification in ART is mainly performed in 2 fashions: daily dose verification and cumulative dose analysis.

Daily Dose Verification

Daily dose verification calculates the radiation dose of the delivered plan on the daily image set. This method focuses on assessing the quality of dose coverage for each fractionated treatment. The most commonly used method of daily dose verification is performing dose recalculation on the daily anatomy, acquired through daily imaging process, and compare the daily dose-volume histogram to fractionated planning dose-volume histogram.

Lee et al[53,54] reported daily dose assessment methods by reconstructing delivered dose with MLC dynalog files and with leaf sequence measured by an electronic portal imaging device. These methods take into consideration the actual MLC positions during the treatment and recalculate the dose in the treatment planning system with the actual measured fluence. Small differences between delivered and planned fluence maps were reported, as well as between delivered and planned dose, except for "discernible differences" in a high-dose region and maximal dose. Dose reconstructions by Monte Carlo methods have also been reported by various research groups using LINAC MLC dynalog files[55] and portal beam measurements.[56]

Cumulative Dose Analysis

Contrary to daily dose verification, cumulative dose analysis focuses on the accumulated dose distribution up to the current fraction. Yan et al[14] developed a model to construct the cumulative dose in a deforming the organ of interest using deformable registration techniques based on a biomechanical model of the elastic body. Wu et al[33] used this cumulative dose analysis model and developed a weekly dose compensation scheme for the deficit in actual delivered dose. By performing volume-element tracking, the discrepancy in doses delivered to each subvolume is identified and compensated in future fractions through plan adaptation. O'Daniel et al[57] evaluated the difference between planned and delivered dose to parotid gland and target using cumulative dose analysis via deformable image registration. Rosu et al[58] investigated the impact of interpolation methods and grid size on the cumulative dose accuracy via deformable registration.

Currently, accurate dose accumulation requires carefully validated deformable registration techniques and complicated workflow. The increased burden and uncertainty in accuracy has been a limiting factor for clinical implementation of cumulative dose analysis, and this needs to be addressed through technology advancement and system integration.[59]

CLINICAL APPLICATION OF ART

Since the early work of ART by Yan et al,[31] the advantage of ART has been increasingly explored by physicians and clinical physicists, who have constantly pushed forward the clinical implementation of different ART techniques. The following is a summary of current ART clinical applications for each specific disease site.

Prostate Cancer

The ART technique has been clinically implemented for prostate cancer treatment in some institutions. Because of its nature of being adjacent to the bladder and the rectum, the prostate region can exhibit significant position/volume change interfractionally,[60] especially when treating both prostate and seminal vesicles, which is found to move largely independently.[61] Xia et al[62] reported 1 clinical case of concurrent prostate and pelvic lymph nodes treatment with the multiple adaptive plan (MAP) strategy. The MAP generates plans for a number of potential prostate locations determined using daily image guidance. For each fraction, the patient was treated with the pregenerated plan that closest matched the daily prostate position. Dosimetric analysis indicated that the MAP technique is beneficial for pelvic lymph nodes coverage but is insufficient to provide complete coverage for the prostate. The offline reoptimization technique[32,52,63] has been clinically implemented at William Beaumont Hospitals.[63–68] The outcome analysis on a large number of patients (>1000) demonstrates improved biochemical control[64,69] and less normal tissue toxicity.[64,70] The Netherlands Cancer Institute implemented an offline adaptive strategy based on planning CT and several repeated CT/CBCT scans but taking into consideration the average position of rectal walls as well.[38,71] In their reported clinical study with 20 patients, the ART protocol was able to reduce PTV volume by an average of 29% and V65 Gy for rectum by an average of 19%.[37] Clinical implementation of ART with online reoptimization is currently limited because of the extra burden of quality assurance (QA) and plan approval associated with modified plans.

Head and Neck

Head and neck is another site that would greatly benefit from ART because of the potentially significant volume change in both target and normal tissue/glands owing to the weight loss experienced by patients. In a study by Barker et al[72] with in-room CT scans on 14 patients, the average GTV loss at the end of the treatment course was 69.5%. Parotid glands also experience considerable volume change and found to lose more than 25% at the end of treatment by Barker et al[72] and Wang et al.[73] Head and neck ART based on offline reoptimization has been implemented at the MD Anderson Cancer Center for treating oropharyngeal cancer. Schwartz and Dong[74] reported the preliminary analysis result on 22 patients with 724 daily CT scans. The patients receive 1 or 2 replan(s) during the treatment course. Retrospective dosimetric analysis reveals that, compared with IGRT alone, 1 replan reduces the mean dose to contralateral and ipsilateral parotid glands by an average of 2.8% and 3.9%, respectively, and 3.8% and 9% for patients with 2 replans. Integral body doses at the 60 and 40 Gy levels were also reduced significantly. A retrospective study by Wu et al[75] systematically evaluated the impact of shrinkage on the dosimetry of target and critical structures, as well as the benefit of replanning. The shrinkage was found to result in small difference between planned and delivered dose in the targets and critical structures, except for an approximately 10% increase in the mean dose to the parotid glands. The combination of replanning and margin reduction was found to provide up to a 30% reduction in the mean cumulative dose to the parotid glands. The clinical outcome of head and neck ART has yet to be reported. The full clinical implementation of ART for head and neck cancer is still limited and requires improvement in both technology and practical guidelines before becoming a new standard.[74,76]

Other Disease Sites

Although most research on ART focuses on prostate and head-and-neck cancer, researchers and clinical groups have also reported using ART in other disease sites. Pos and Pos[77] summarized the technologies in bladder cancer ART. One offline, clinically adaptive, partial-bladder radiotherapy using CT scans reported by The Netherlands Cancer Institute group was found to provide adequate GTV coverage while reducing treatment volumes by 40%. Adaptive radiation therapy for lung cancer is primarily focused on addressing intrafractional motion, for example, through constructing and optimizing internal tumor volume, but less on interfractional motion[78]; an offline adaptive process for non–small cell lung cancer has been implemented in William Beaumont Hospital, in which target motion measured by four-dimensional CT and is used to determine the patient-specific target margin required for the CTV exceeds 99.9% of prescription doses.[79,80] Similar margin management has also been developed and implemented at the MD Anderson Cancer Center.[81] Brock and Dawson[82] and Tanderup et al[83] reported the development of an adaptive management for liver and cervical cancer treatments, respectively, but clinical application of ART in these 2 sites is still limited.

CHALLENGES AND FUTURE WORK

The development in imaging and reoptimization algorithm has made it possible to personalize radiation therapy and to follow the dynamically changing anatomy throughout the treatment course. However, fully integrating ART into clinical practice still faces several challenges:

CBCT Image Quality and CT Number Consistency

For online image guidance, CBCT has been a valuable tool to acquire image with the patient in treatment position. However, because of the higher scatter and less mechanical stability, the image quality of CBCT is still inferior from planning CT. As one of the key component of many ART systems, deformable registration relies heavily on the quality of CBCT images to provide accurate result. In prostate cases where low-contrast soft tissue dominates, high-contrast soft tissue and low artifacts are essential for producing acceptable deformation accuracy. In addition, the CT number in CBCT images has a small but noticeable difference from planning CT for the same materials.[84,85] This inconsistency could result in differences between dose calculated on CT and CBCT owing to inhomogeneity correction. Although a dedicated calibration curve may reduce the inconsistency to an acceptable level,[84,85] additional effort is required to generate and maintain the calibration curves for each CBCT unit, especially for centers with multiple CBCTs.

Clinical Resource Management

The main obstacle limiting ART from wide clinical implementation is the time management challenge. Many components in the proposed ART process require considerably increased cost to time and staff resources compared with current IGRT technique and are therefore difficult to be integrated into the clinical flow for each patient. These added costs to recourses come from daily structure contouring, reoptimization, patient-specific QA, and plan evaluation and approval. The key to address this challenge is through improving computational speed and automation. Recent development in these components has shown great promise to increase the efficiency. Automatic contour propagation through deformable registration can be performed by commercially available tools such as Velocity I (Velocity Medical Solutions, Atlanta, GA). GPU-accelerated deformable registration engine developed by Gu et al[76] is capable of finishing registration within 7 to 11 seconds. Fast reoptimization algorithm with linear programming,[8] 2-step "SAM + SWO" algorithm,[48] and GPU acceleration[49] reduces the time of reoptimization to 1 to 2 minutes, less than 6 minutes, and 3.8 seconds, respectively. Advanced QA technique using MLC and Monte Carlo technology has also been reported by Teke et al.[55] It is envisioned that near real-time online ART is possible in the near future through combination and continuous development of these technologies.

System Integration

For ART to become standard clinical practice in radiation therapy, unified and seamless integration of all ART components into treatment planning system and clinical record and verify system is essential. This requires close collaboration between researchers and vendors. Until then, extreme caution should be placed in the clinical deployment of ART techniques to minimize mistakes and ensure patient safety.

REFERENCES

1. *ICRU-50 1993. Prescribing, Recording and Reporting Photon Beam Therapy.* Bethesda, MD: International Commission on Radiation Units and Measurements.
2. Yoo DS, Wong TZ, Brizel DM. The role of adaptive and functional imaging modalities in radiation therapy: approach and application from a radiation oncology perspective. *Semin Ultrasound CT MR*. 2010;31: 444–461.
3. Court L, Rosen I, Mohan R, et al. Evaluation of mechanical precision and alignment uncertainties for an integrated CT/LINAC system. *Med Phys*. 2003;30:1198–1210.
4. Court LE, Dong L. Automatic registration of the prostate for computed-tomography–guided radiotherapy. *Med Phys*. 2003;30:2750–2757.
5. 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;62:154–163.
6. 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;51:2493–2501.
7. 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;55:428–435.
8. Wu QJ, Thongphiew D, Wang Z, et al. On-line re-optimization of prostate IMRT plans for adaptive radiation therapy. *Phys Med Biol*. 2008;53: 673–691.
9. Lei Y, Wu Q. A hybrid strategy of offline adaptive planning and online image guidance for prostate cancer radiotherapy. *Phys Med Biol*. 2010;55: 2221–2234.
10. de la Zerda A, Armbruster B, Xing L. Formulating adaptive radiation therapy (ART) treatment planning into a closed-loop control framework. *Phys Med Biol*. 2007;52:4137–4153.
11. Jaffray DA, Siewerdsen JH, Wong JW, et al. Flat-panel cone-beam computed tomography for image-guided radiation therapy. *Int J Radiat Oncol Biol Phys*. 2002;53:1337–1349.
12. Langen KM, Zhang Y, Andrews RD, et al. Initial experience with megavoltage (MV) CT guidance for daily prostate alignments. *Int J Radiat Oncol Biol Phys*. 2005;62:1517–1524.
13. Ruchala KJ, Olivera GH, Schloesser EA, et al. Megavoltage CT on a tomotherapy system. *Phys Med Biol*. 1999;44:2597–2621.
14. Yan D, Jaffray DA, Wong JW. A model to accumulate fractionated dose in a deforming organ. *Int J Radiat Oncol Biol Phys*. 1999;44:665–675.
15. Coselmon MM, Balter JM, McShan DL, et al. Mutual information based CT registration of the lung at exhale and inhale breathing states using thin-plate splines. *Med Phys*. 2004;31:2942–2948.
16. 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;50:2887–2905.
17. Lu W, Olivera GH, Chen Q, et al. Deformable registration of the planning image (kVCT) and the daily images (MVCT) for adaptive radiation therapy. *Phys Med Biol*. 2006;51:4357–4374.
18. Kashani R, Hub M, Balter JM, et al. Objective assessment of deformable image registration in radiotherapy: a multi-institution study. *Med Phys*. 2008;35:5944–5953.
19. Cao Y, Popovtzer A, Li D, et al. Early prediction of outcome in advanced head-and-neck cancer based on tumor blood volume alterations during therapy: a prospective study. *Int J Radiat Oncol Biol Phys*. 2008;72: 1287–1290.
20. Craciunescu OI, Blackwell KL, Jones EL, et al. DCE-MRI parameters have potential to predict response of locally advanced breast cancer patients to neoadjuvant chemotherapy and hyperthermia: a pilot study. *Int J Hyperthermia*. 2009;25:405–415.
21. Mayr NA, Wang JZ, Zhang D, et al. Longitudinal changes in tumor perfusion pattern during the radiation therapy course and its clinical impact in cervical cancer. *Int J Radiat Oncol Biol Phys*. 2010;77: 502–508.
22. Dimopoulos JC, Schirl G, Baldinger A, et al. MRI assessment of cervical cancer for adaptive radiotherapy. *Strahlenther Onkol*. 2009;185: 282–287.
23. Schuetz M, Schmid MP, Potter R, et al. Evaluating repetitive ^{18}F-fluoroazomycin-arabinoside (^{18}FAZA) PET in the setting of MRI guided adaptive radiotherapy in cervical cancer. *Acta Oncol*. 2010;49:941–947.
24. Fallone BG, Murray B, Rathee S, et al. First MR images obtained during megavoltage photon irradiation from a prototype integrated LINAC-MR system. *Med Phys*. 2009;36:2084–2088.
25. Geets X, Tomsej M, Lee JA, et al. Adaptive biological image-guided IMRT with anatomic and functional imaging in pharyngo-laryngeal tumors: impact on target volume delineation and dose distribution using helical tomotherapy. *Radiother Oncol*. 2007;85:105–115.
26. Roper J, Bowsher J, Yin FF. On-board SPECT for localizing functional targets: a simulation study. *Med Phys*. 2009;36:1727–1735.
27. Chung PW, Haycocks T, Brown T, et al. On-line aSi portal imaging of implanted fiducial markers for the reduction of interfraction error during conformal radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys*. 2004;60:329–334.
28. Barney BM, Lee RJ, Handrahan D, et al. Image-guided radiotherapy (IGRT) for prostate cancer comparing kV imaging of fiducial markers with cone beam computed tomography (CBCT). *Int J Radiat Oncol Biol Phys*. 2011;80:301–305.
29. Wu Q, Ivaldi G, Liang J, et al. Geometric and dosimetric evaluations of an online image-guidance strategy for 3D-CRT of prostate cancer. *Int J Radiat Oncol Biol Phys*. 2006;64:1596–1609.
30. Shi W, Li JG, Zlotecki RA, et al. Evaluation of kV cone-beam CT performance for prostate IGRT: a comparison of automatic grey-value alignment to implanted fiducial-marker alignment. *Am J Clin Oncol*. 2011;34:16–21.
31. Yan D, Vicini F, Wong J, et al. Adaptive radiation therapy. *Phys Med Biol*. 1997;42:123–132.
32. Yan D, Lockman D, Brabbins D, et al. An off-line strategy for constructing a patient-specific planning target volume in adaptive treatment

process for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2000;48: 289–302.
33. Wu Q, Liang J, Yan D. Application of dose compensation in image-guided radiotherapy of prostate cancer. *Phys Med Biol*. 2006;51: 1405–1419.
34. Birkner M, Yan D, Alber M, et al. Adapting inverse planning to patient and organ geometrical variation: algorithm and implementation. *Med Phys*. 2003;30:2822–2831.
35. Rehbinder H, Forsgren C, Lof J. Adaptive radiation therapy for compensation of errors in patient setup and treatment delivery. *Med Phys*. 2004;31:3363–3371.
36. Wu C, Jeraj R, Lu W, et al. Fast treatment plan modification with an over-relaxed Cimmino algorithm. *Med Phys*. 2004;31:191–200.
37. Nijkamp J, Pos FJ, Nuver TT, et al. Adaptive radiotherapy for prostate cancer using kilovoltage cone-beam computed tomography: first clinical results. *Int J Radiat Oncol Biol Phys*. 2008;70:75–82.
38. Nuver TT, Hoogeman MS, Remeijer P, et al. An adaptive off-line procedure for radiotherapy of prostate cancer. *Int J Radiat Oncol Biol Phys*. 2007;67:1559–1567.
39. Mackie TR, Balog J, Ruchala K, et al. Tomotherapy. *Semin Radiat Oncol*. 1999;9:108–117.
40. Wu C, Jeraj R, Olivera GH, et al. Re-optimization in adaptive radiotherapy. *Phys Med Biol*. 2002;47:3181–3195.
41. Welsh JS, Lock M, Harari PM, et al. Clinical implementation of adaptive helical tomotherapy: a unique approach to image-guided intensity modulated radiotherapy. *Technol Cancer Res Treat*. 2006;5:465–479.
42. Woodford C, Yartsev S, Dar AR, et al. Adaptive radiotherapy planning on decreasing gross tumor volumes as seen on megavoltage computed tomography images. *Int J Radiat Oncol Biol Phys*. 2007;69:1316–1322.
43. Song WY, Wong E, Bauman GS, et al. Dosimetric evaluation of daily rigid and nonrigid geometric correction strategies during on-line image-guided radiation therapy (IGRT) of prostate cancer. *Med Phys*. 2007;34: 352–365.
44. Mohan R, Zhang X, Wang H, et al. Use of deformed intensity distributions for on-line modification of image-guided IMRT to account for interfractional anatomic changes. *Int J Radiat Oncol Biol Phys*. 2005;61: 1258–1266.
45. Fu W, Yang Y, Yue NJ, et al. A cone beam CT-guided online plan modification technique to correct interfractional anatomic changes for prostate cancer IMRT treatment. *Phys Med Biol*. 2009;54:1691–1703.
46. Feng Y, Castro-Pareja C, Shekhar R, et al. Direct aperture deformation: an interfraction image guidance strategy. *Med Phys*. 2006;33: 4490–4498.
47. Thongphiew D, Wu QJ, Lee WR, et al. Comparison of online IGRT techniques for prostate IMRT treatment: adaptive vs repositioning correction. *Med Phys*. 2009;36:1651–1662.
48. Ahunbay EE, Peng C, Holmes S, et al. Online adaptive replanning method for prostate radiotherapy. *Int J Radiat Oncol Biol Phys*. 2010; 77:1561–1572.
49. Men C, Jia X, Jiang SB. GPU-based ultra-fast direct aperture optimization for online adaptive radiation therapy. *Phys Med Biol*. 2010;55: 4309–4319.
50. Li T, Thongphiew D, Zhu X, et al. Adaptive prostate IGRT combining online reoptimization and re-positioning: a feasibility study. *Phys Med Biol*. 2011;56:1243–1258.
51. Li T, Zhu X, Thongphiew D, et al. On-line adaptive radiation therapy: feasibility and clinical study . *J Oncol*. 2010b;2010;407236.
52. Yan D. Adaptive radiotherapy: merging principle into clinical practice. *Semin Radiat Oncol*. 2010;20:79–83.
53. Lee L, Le QT, Xing L. Retrospective IMRT dose reconstruction based on cone-beam CT and MLC log-file. *Int J Radiat Oncol Biol Phys*. 2008;70:634–644.
54. Lee L, Mao W, Xing L. The use of EPID-measured leaf sequence files for IMRT dose reconstruction in adaptive radiation therapy. *Med Phys*. 2008;35:5019–5029.
55. Teke T, Bergman AM, Kwa W, et al. Monte Carlo based, patient-specific rapid arc QA using LINAC log files. *Med Phys*. 2010;37:116–123.
56. van Elmpt WJ, Nijsten SM, Schiffeleers RF, et al. A Monte Carlo based three-dimensional dose reconstruction method derived from portal dose images. *Med Phys*. 2006;33:2426–2434.
57. 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: 1290–1296.
58. Rosu M, Chetty IJ, Balter JM, et al. Dose reconstruction in deforming lung anatomy: dose grid size effects and clinical implications. *Med Phys*. 2005;32:2487–2495.
59. Jaffray DA, Lindsay PE, Brock KK, et al. Accurate accumulation of dose for improved understanding of radiation effects in normal tissue. *Int J Radiat Oncol Biol Phys*. 2010;76:S135–S139.
60. Li T, Zhu X, Thongphiew D, et al. On-line adaptive radiation therapy (ART): feasibility and clinical study. [Published online ahead of print November 22, 2010.] *J Oncol*.
61. Liang J, Wu Q, Yan D. The role of seminal vesicle motion in target margin assessment for online image-guided radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2009;73:935–943.
62. Xia P, Qi P, Hwang A, et al. Comparison of three strategies in management of independent movement of the prostate and pelvic lymph nodes. *Med Phys*. 2010;37:5006–5013.
63. Martinez AA, Yan D, Lockman D, et al. Improvement in dose escalation using the process of adaptive radiotherapy combined with three-dimensional conformal or intensity-modulated beams for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2001;50:1226–1234.
64. Ghilezan M, Yan D, Martinez A. Adaptive radiation therapy for prostate cancer. *Semin Radiat Oncol*. 2010;20:130–137.
65. Yan D, Birkner M, Nuesslin F, et al. Improvement in dose escalation using off-line & on-line image feedback in the intensity modulated beam design for prostate cancer treatment. *Int J Radiat Oncol Biol Phys*. 2001; 51:91–92.
66. Brabbins D, Martinez A, Yan D, et al. A dose-escalation trial with the adaptive radiotherapy process as a delivery system in localized prostate cancer: analysis of chronic toxicity. *Int J Radiat Oncol Biol Phys*. 2005;61: 400–408.
67. Harsolia A, Vargas C, Yan D, et al. Predictors for chronic urinary toxicity after the treatment of prostate cancer with adaptive three-dimensional conformal radiotherapy: dose-volume analysis of a phase II dose-escalation study. *Int J Radiat Oncol Biol Phys*. 2007;69:1100–1109.
68. Vargas C, Yan D, Kestin LL, et al. Phase II dose escalation study of image-guided adaptive radiotherapy for prostate cancer: use of dose-volume constraints to achieve rectal isotoxicity. *Int J Radiat Oncol Biol Phys*. 2005;63:141–149.
69. Brabbins DS, Kestin L, Yan D, et al. Improvement in clinical outcomes with prostate radiotherapy at a single institution in the PSA era. *Int J Radiat Oncol Biol Phys*. 2008;72:S318–S319.
70. Ghilezan M, Yan D, Martinez A. *Image-Guided Radiation Therapy of Prostate Cancer*. Valicenti RK, et al, ed. New York, NY: Information Healthcare; 2008.
71. Hoogeman MS, van Herk M, de Bois J, et al. Strategies to reduce the systematic error due to tumor and rectum motion in radiotherapy of prostate cancer. *Radiother Oncol*. 2005;74:177–185.
72. 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;59:960–970.
73. 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;119:1966–1974.
74. Schwartz DL, Dong L. Adaptive radiation therapy for head and neck cancer—can an old goal evolve into a new standard? [Published online ahead of print August 18, 2010.] *J Oncol*.
75. 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;75:924–932.

76. Castadot P, Lee JA, Geets X, et al. Adaptive radiotherapy of head and neck cancer. *Semin Radiat Oncol*. 2010;20:84–93.
77. Pos F, Remeijer P. Adaptive management of bladder cancer radiotherapy. *Semin Radiat Oncol*. 2010;20:116–120.
78. Sonke JJ, Belderbos J. Adaptive radiotherapy for lung cancer. *Semin Radiat Oncol*. 2010;20:94–106.
79. Yan D, Lockman D, Martinez A, et al. Computed tomography guided management of interfractional patient variation. *Semin Radiat Oncol*. 2005;15:168–179.
80. Liang J, Yan D, Kestin LL, et al. Minimization of target margin by adapting treatment planning to target respiratory motion. *Int J Radiat Oncol Biol Phys*. 2003;57:S233–S234.
81. Gomez DR, Chang JY. Adaptive Radiation for Lung Cancer. [Published online ahead of print August 4, 2010.] *J Oncol*.
82. Brock KK, Dawson LA. Adaptive management of liver cancer radiotherapy. *Semin Radiat Oncol*. 2010;20:107–115.
83. Tanderup K, Georg D, Potter R, et al. Adaptive management of cervical cancer radiotherapy. *Semin Radiat Oncol*. 2010;20:121–129.
84. Yang Y, Schreibmann E, Li T, et al. Evaluation of on-board kV cone beam CT (CBCT)–based dose calculation. *Phys Med Biol*. 2007;52:685–705.
85. Yoo S, Yin FF. Dosimetric feasibility of cone-beam CT-based treatment planning compared to CT-based treatment planning. *Int J Radiat Oncol Biol Phys*. 2006;66:1553–1561.