A Review of Online Adaptive Radiation Therapy

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Abstract

Advances in cone-beam CT (CBCT) and MRI, together with rapid and accurate tissue segmentation and treatment planning accelerated by artificial intelligence and machine learning, have made online adaptive radiation therapy (ART) feasible on commercial radiation therapy systems. In this review, we examine the status of CBCT- and MRI-based online ART in light of their recent increase in clinical adoption.

Keywords: adaptive radiation therapy, CBCT, MRI

Introduction

With technology advancements and contour standardization, errors in imaging, contouring, and treatment setup have been reduced over the last decades. However, errors occur when a singular treatment plan is used over the course of therapy without adjustment for the patient's anatomical changes during that time. Yan proposed the concept of adaptive radiation therapy (ART) to reduce the impact of anatomical changes during therapy and summarized ART as "*a closed loop radiation treatment process where the treatment plan can be modified (including re-optimized) using systematic feedback of measurements (e.g., onboard imaging)*."[1] The goal of ART is to maintain objectives of the initial planning over the course of treatment, during which anatomical change may occur.

Anatomical variations between the initial planning and treatment phases are common in radiation therapy for cancers such as head and neck (HN), lung, prostate, and gastrointestinal cancers. Such variations present in different formats (e.g., tumor shrinkage or progression) and timescale (days to weeks). For example, Kishan et al studied 12 patients with HN and observed a median increase of 16% in the gross target volume between treatment planning and the first treatment (a median of 13 d).[2] Other anatomical changes, such as bladder or rectal filling, peristalsis, and uterus motion, may occur over minutes to hours. Importantly, anatomical variations are often patient-specific and cannot be accurately predicted from population models, warranting the need for ART approaches that can respond to an individual patient's evolving anatomy.

A critical component of ART is onboard imaging (OBI). Ideally, the image quality of OBI should be comparable to that of simulation to ensure accurate adaptation. However, compared with simulation CT (SIM-CT), OBI on a regular linear accelerator (linac), cone-beam CT (CBCT) system produces inferior images that can be characterized by lower soft tissue contrast, greater susceptibility to artifacts, and inaccurate electron density-to-Hounsfield Unit (HU) calibration.

CBCT technology has been improving due to hardware and software advancements. For example, the gantry speed of a Halcyon linac (Varian Medical Systems, Palo Alto, CA) can reach up to 4 rotations per minutes (RPM), which is 4 times faster than that of a Varian TrueBeam linac. This fast rotation allows for a CBCT acquisition within a single breath-hold (BH).[3] The rapid image acquisition, along with an advanced iterative CBCT (iCBCT) reconstruction algorithm, improved

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image quality and consistency of BH-CBCTs.[3] Most recently, Varian introduced the HyperSight CBCT system, making the imaging quality of OBI closer to that of SIM-CT.[4,5] The HyperSight is available for the Varian Ethos system (developed based on the Halcyon system), a platform specifically designed for online ART.

CBCT produces inferior soft tissue contrast compared to MRI. Therefore, a radiation therapy machine equipped with onboard MRI is more desirable for ART, despite the many technical challenges involved in operating the machine in the presence of a strong magnetic field. The first commercial MRI-guided radiation therapy (MRgRT) machine was developed by ViewRay (ViewRay Inc, Oakwood, USA), combining a 0.35 T MRI scanner and 3 Co-60 sources mounted on a ring gantry.[6] In its later design, the Co-60 sources were replaced by a linac for improved treatment effeciency.[7] The Elekta Unity MRI-linac (Elekta, Stockholm, Sweden), FDA cleared in 2023, integrates a 1.5 T MRI scanner with a linac.

In this review, we begin with an overview of offline and online ART before focusing on CBCT- and MRI-based online ART. For CBCT-based online ART, we discuss the workflow, advantages, as well as limitations and futures of the Ethos system. For MRI-based online ART or adaptive MRgRT, we also cover its workflow, advantages and limitations, and conclude with our perspectives on the future of online adaptive MRgRT.

Offline and Online ART

Onboard CBCT may capture progressive anatomical changes, such as tumor progression or shrinkage or those caused by weight loss, enabling the use of offline ART when these changes exceed certain thresholds.[1] Offline ART requires replanning between treatment fractions. Because CBCT lacks the image quality (e.g., artifacts, small field of view, inaccurate HU) needed for treatment planning, repeat simulation is required for offline ART. After resimulation, the workflow of offline ART is similar to that of the initial treatment planning: contouring, planning, physician and physicist review, patient-specific quality assurance (PSQA), pretreatment CBCT verification and correction, and treatment delivery.[8-10] By combining the delivered fractions with the offline-adapted plans, the overall quality of the radiation therapy can be evaluated. Institutional studies and clinical trials, especially in the treatment of prostate cancer and HN cancer, have shown the benefits of offline ART.[11-14] Additionally, repeated functional imaging can be acquired and used to guide dose adjustments based on tumor responses.[15-18] The frequency of offline ART depends on the timescale and magnitude of anatomical variations.

Online ART involves replanning while patients remain in the treatment position. This approach can be further divided into 2 subcategories: plan-of-the-day (PotD) and daily replanning. The PotD method involves creating a library of plans to accommodate potential daily anatomical variations.[19-23] The physician then selects one plan from the library based on the "daily" anatomy of the pretreatment CBCT. The ART using the PotD strategy is also called hybrid ART because the adaptive plan is created offline but the decision for ART is made online. The method of daily replanning requires potential replanning before treatment.[9] The replanning is triggered if target coverage and/or doses to organs-at-risk (OARs) exceed clinically acceptable errors (mostly by physician's decision). By default, daily replanning strategy is referred to as online ART, which we will focus on in this review.

Despite potentially better patient outcomes, online ART is more time-consuming and resource-intensive than conventional RT or offline ART.[10,23-31] A dedicated team is required to quickly and accurately review and approve daily contours and new plans, and to conduct QAs.

Appropriate patient selection is critical to the success of online ART, which is well suited for cases with noticeable inter-fractional but few intra-fractional anatomical variations. Real-time ART,[32,33] beyond the scope of this review, could be useful for mitigating the impacts of fast intra-fractional tissue variations.

CBCT-Based Online ART

The Varian Ethos system provides a platform to perform online ART in as little as 15 minutes, which is achieved by using rapid, high-quality CBCT, as well as artificial intelligence (AI) and machine learning (ML).[34-37]

The Ethos system uses a fast gantry (4 RPM) and a novel iterative (iCBCT) reconstruction method to generate high-quality CBCT.[37,38] It employs AI and ML to expedite tissue segmentation and plan optimization and GPUs to accelerate dose calculations. The Ethos system is an O-ring linac equipped with a 6 MV Flattening Filter Free beam at a maximum dose rate of 800 monitor units per minute (MU/min).[37] A dual-layer multileaf collimator allows for the delivery of both intensity-modulated radiation therapy and volumetric-modulated arc therapy.

Workflow

The workflow of online ART on the Ethos system starts with an approved treatment plan called the "reference plan." At each treatment session, a CBCT is acquired that can be reconstructed using iCBCT or a conventional Feldkamp-Davis-Kress (FDK) algorithm. For adaptive, or "intent" planning, a certain set of contours called "influencers" are automatically generated using either an AI-based or deformable image registration (DIR)-based method. The influencer structures are typically structures near or within the target. A structure-guided DIR is applied from the planning CT to the CBCT to create a synthetic CT (sCT) for dose calculation. After the influencer review, target volumes may be propagated onto the pretreatment CBCT and reviewed by the physician. The Ethos system then generates 2 types of plans: a "scheduled plan" by calculating the fluence from the reference plan onto the sCT and an "adaptive plan" using an intelligent optimization engine with the "daily" contours. The physician compares the scheduled and adaptive plans in terms of dose-volume histogram (DVH) metrics and dose distributions, and decides which plan is used for treatment. Subsequently, a qualified medical physicist performs the MU verification using Varian Mobius3D. An optional CBCT can be acquired to verify the final treatment position and evaluate for changes in internal anatomy. **Table 1** provides the summary of the workflow of nonadaptive and adaptive planning after the acquisition of SIM-CT.

Advantages

The Ethos system uses onboard CBCT for ART. Because CBCT is widely used for image-guided radiation therapy, the implementation of Ethos online ART may not require major changes to the existing infrastructure or neecessitate staff training on a completely new technology like MRI-based online ART.

The Ethos iCBCT offers a higher contrast-to-noise ratio than conventional CBCT, enabling an improved accuracy in soft tissue delineation and dose calculation. The Ethos 2.0 with HyperSight CBCT further enhances its iCBCT performance with faster acquisition time (6 s), a larger field of view (up to 70 cm), and a newly designed kV detector. Users may directly replan on HyperSight iCBCT, eliminating the need for sCT.

Many centers have implemented online ART using the Ethos system for many disease sites[14,26,27,29,35-44] and have shown improved target and/or OAR sparing. For a study in advanced pancreatic cancer, Schiff found that 100% of adapted fractions (40) met the OAR constraints while only 1 out of 40 nonadapted fractions met all OAR constraints.[44] In addition, the Ethos system allows for safe dose escalation in certain cases, which could potentially lead to improved tumor control rates. For online ART, the Ethos system is more cost-effective and offers shorter treatment than MRI-based systems.

Current Challenges and Future Perspectives

The implementation of online ART using the Ethos system is different from conventional CBCT-guided RT in terms of software, hardware, and workflows. The new approach requires considerable resources (especially in personnel) and thus presents a great challenge for its adoption.[37] Because online ART requires skilled staff to rapidly and accurately assess a patient's daily anatomical changes, make appropriate plan adjustments, and ensure QA during the treatment session, at least one dedicated medical physicist should be present for the majority of the workday to accommodate patient load.[37,43] A physician needs to be present for plan and contour review and approval.

Although AI and automation improve the efficiency of online ART on Ethos, the treatment can take more than 30 minutes for certain disease sites and for specific patients. The prolonged time on the couch may result in changes to the patient's anatomy, requiring the process to be restarted in the worst scenario.

The Ethos system operates as a black box, and some QA methods for regular linacs are not available . Many built-in QA tools are from Varian (e.g., Mobius3D). Although, retrospectively, the dosimetric and contouring accuracy has been verified,[43,45] there is a need for independent and quick QA solutions for plan checks and secondary dose calculations to guarantee patient safety and treatment accuracy.[46]

Although several studies have demonstrated the dosimetric advantages of online ART in terms of improved target coverage and reduced dose to OARs, more robust prospective clinical trials are needed to establish the impact of online ART on treatment outcomes. Future research also needs to focus on identifying which patient populations and disease sites would benefit most from online ART to optimize resource allocation and ensure cost-effectiveness.[47]

MRI-Based Online Adaptation

Recent technology advancements have made MRgRT a reality by integrating an MRI scanner with a linac or a Co-60 machine.[48] The first commercial MRgRT system, the ViewRay MRIdian system, was installed at Washington University in St. Louis, and the treatment of patients started in January 2014.[6] This machine combined a 0.35 T superconducting MRI scanner with 3 Co-60 heads mounted on a ring gantry, with MRI and RT system sharing the same isocenter. Later models of the MRIdian replaced the Co-60 design with

Table 1. Workflows of Nonadaptive and Adaptive Planning

	NONADAPTIVE	ADAPTIVE
Image registration	Rigid registration between the daily CBCT and the SIM-CT	DIR-based registration between the daily CBCT and the SIM-CT
Contour updates	DIR- or AI-based daily contours	DIR- or AI-based daily contours
Optimization	NO	Plan is reoptimized based on the updated "daily contours"
Plan adaptation	Plan is calculated using the fluence of the original plan on the sCT	Plan is recalculated on the sCT after optimization

Abbreviations: AI, artificial intelligence; CBCT, cone beam CT; DIR, deformable image registration; sCT, synthetic CT; SIM-CT, simulation CT.

a linac for enhanced treatment capabilities. In 2017, the first person was treated using the MRIdian linac system .[7] Another commercial MRgRT system, the Elekta Unity, was developed by Elekta in partnership with Philips (Philips, Amsterdam, the Netherlands).[49] It integrates a 1.5 T MRI scanner with a linac equipped with 6 MV beams. The higher magnetic field strength produces diagnostic-quality imaging. With other systems in the development phase,[50,51] MRgRT introduces a new paradigm in treatment planning, real-time monitoring, and online ART.[52,53]

Workflow

An efficient workflow is essential for implementing online adaptive MRgRT. After the target and OAR delineation on CT or MR simulation, a reference plan is created to meet the dosimetric criteria. At each treatment session, a daily MRI is acquired prior to the treatment. According to the anatomy changes in the target and OARs between the pretreatment MRI and simulation image, one of the two workflows can be executed. If the anatomy of target and OAR is sustained, the "adapt to position" workflow is applied. The daily MRI is first aligned with the simulation image based on rigid registration, and an isocenter shift is implemented. The couch is then translated for the ViewRay system or a virtual couch shift is utilized for the Unity system. If necessary, an adaptive plan can be generated by applying segment adaptation or optimization to further enhance plan dosimetry. These adaptive plans are still based on the simulation images. However, if the anatomical changes are significant, the second method, "adapt to shape," is applied.[54-56] The daily MRI and simulation images are first aligned using deformable registration. The original ROIs and plan are propagated to the daily MRI, and new contours of the target and OARs are modified or delineated on the daily MRI. The electron density is assigned to each organ on the MRI generated sCT, and an adaptive plan is generated by adjusting or re-optimizing fluence. A summary of the above adaptive workflows is listed in **Table 2**.

Advantages

With superior soft tissue contrast and continuous intrafractional imaging, an MRgRT system could be ideal for online ART.[54-58] Studies show that physicians prefer reoptimized plans in over 90% of cases.[59,60] Unlike CBCT, MRI is nonionizing radiation, enhancing patient safety for treatments requiring frequent imaging. Moreover, MRgRT enables physicians to directly monitor tumor motion without relying on surrogates, reducing alignment errors particularly in areas prone to movement (e.g., abdomen and thorax). This capability allows more precise dose delivery to the target while sparing surrounding healthy tissues, resulting in fewer side effects. For example, patients with prostate cancer treated with online adaptive MRgRT experienced lower rates of gastrointestinal and genitourinary toxicity than those treated with conventional approaches.[61-63] Emerging data suggest that online adaptive MRgRT enables safe dose escalation in the treatment of pancreatic, prostate, and lung cancer.[64-68]

Because onboard MRI provides accurate volumetric imaging for each treatment, it enables precise calculation of the cumulative dose to organs from each fraction. This detailed volumetric dose mapping allows clinicians to monitor dose constraints and make adjustment if limits are exceeded.[69,70] Understanding the exact dose distribution of organs and their specific subregions is essential for assessing potential toxicities. Voxel-by-voxel data of daily dose offer valuable insights into normal tissue tolerance.[71,72]

Beyond current MRgRT, functional MRI on an MRI-linac enables the potential of biological guidance RT. Studies indicate that conventional RT can leave radioresistant portions of the tumor undertreated due to tumor heterogeneity, contributing to recurrence.[73] Online adaptive functional MRgRT allows clinicians to obtain biological insights on specific subvolumes within the tumor, facilitating patient-specific, heterogeneous dosing strategies that potentially improve therapeutic outcomes.[74-76]

Table 2. Workflows of "Adapt to Position" and "Adapt to Shape" in Adaptive MRI-Guided Radiation Therapy

	ADAPT TO POSITION	ADAPT TO SHAPE
Image registration	Align the daily MRI rigidly to the SIM-CT	Align the daily MRI deformably to the SIM-CT
Contour updates	Use original contours with updated ISO	• Use adapted contours • Assign electron density based on the daily MRI
Segment or fluence optimization	• Use the original segments • Adapt the segments • Optimize segments' weights	• Optimize fluence weights • Adjust fluence shape
Plan adaptation	Recalculate or reoptimize the original plan on the SIM-CT	Recalculate or reoptimize the plan on the online MRI

Abbreviations: SIM-CT, simulation CT.

Current Challenges

Implementing an online adaptive MRgRT program demands considerable investment in capital (significantly more than the in the Ethos system) and personnel, which presents a substantial barrier to its adoption.[61,77]

Integrating an MRI scanner with a linac is complex and comes with inherent limitations. Both components require modification from their conventional forms, resulting in compromised performance compared with their stand-alone counterparts.[53,78] Commercial MRI-linacs use lower magnetic field strength than diagnostic MRI scanners (1.5 T to 7 T) to mitigate the electron return effect,[79] resulting in inferior image quality. Because the moving linac gantry disrupts magnetic field homogeneity, most MRI-linacs only allow step-and-shoot delivery.[49,80] Additionally, beam configuration is restricted to coplanar angles due to system geometry and beam energy is limited to low energies such as Co-60, 6 MV, and 7 MV.

Another critical concern for online adaptive MRgRT is image distortion as accurate volumetric target delineation and precise location mapping are essential for beam positioning. The MRI scanner in an MRI-linac requires larger volumetric coverage and off-isocenter imaging than a diagnostic scanner, which complicates achieving a homogeneous magnetic field.[81-83] Image distortion is less pronounced at 0.35 T,[56] but in high-field systems like the 1.5 T Elekta Unity, it becomes a greater challenge. Techniques such as field correction, B0 mapping, and local shimming can improve image quality, although shimming becomes particularly challenging with moving components like the gantry.[7,53]

Online adaptive MRgRT is time-consuming not only because MRI is inherently slow but also due to the multistep adaptation process. Studies indicate that online adaptation can extend RT sessions by 30 to 60 minutes, impacting treatment efficiency and thus throughput.[84,85] Like CBCT-based ART, the extended duration may also increase patient discomfort and the risk of undesired intra-fractional motion, potentially compromising the accuracy of replanning. Given its low cost-effectiveness, appropriate patient selection is crucial. Patients who are most likely to benefit should be prioritized for MRgRT, such as those with tumors that are difficult to visualize or delineate using CBCT or are located near critical structures.

Future Perspectives

One promising direction for adaptive MRgRT involves the use of quantitative MRI-derived biomarkers, which can provide valuable insights into treatment response and enable more personalized radiation therapy for potentially improving outcomes. Dynamic contrast-enhanced MRI, which measures tissue perfusion and permeability, allows clinicians to detect microvascular changes that could indicate early responses or resistance to treatment.[86,87] This technique is valuable in evaluating cancers such as HN and prostate cancer,[88,89] where early response indicators could be crucial. Quantitative assessment of T1 and T2 relaxation times shows promise in predicting prostate radiation therapy response.[90] Chemical exchange saturation transfer MRI can quantify chemical components, with amide proton transfer helping distinguish true progression from pseudoprogression in glioma.[91] These quantitative MRI tools provide valuable noninvasive insights into tissue function, structure, and physiology, revealing tumor heterogeneity, hypoxia characteristics, and treatment response. All this information helps identify heterogeneous targets and support the feasibility of dose escalation in more aggressive or radioresistant disease areas.

Rapid MRI techniques are essential to achieve comprehensive quantitative measurement. Emerging fast MRI techniques significantly reduce imaging acquisition times through advanced reconstruction algorithms for sparsity acquisitions, such as parallel imaging and compressed sensing.[92,93] MR fingerprinting, a novel, ultrafast quantitative method, enables simultaneous measurement of multiple parameters, demonstrating great potential for distinguishing diverse tissue characteristics.[94-97] Moreover, AI and ML are increasingly being adopted to accelerate MRI reconstruction.[98,99]

Online adaptive MRIgRT transforms the conventional workflow in radiation therapy, introducing many intensive tasks requiring AI assistance for time saving without compromising the treatment accuracy during daily treatment.[100-103] Additionally, accurate dose accumulation over daily treatments requires robust DIR and precise dose-mapping methods, both of which can also benefit from advancements in AI techniques. Real voxel-by-voxel daily dose assessments enable continuous tracking therapeutic doses for targets and normal tissue tolerances, providing valuable data to further guide future treatments.[69,70]

It is worth mentioning that the true potential of MRgRT is not merely the increase in target coverage and reduction of toxicity, which may likely improve clinical outcomes for local control and survival rate. More importantly, it opens opportunities to address complex scenarios, such as ultra-dose escalation in areas with large motion or cases in close proximity to critical organs, and reirradiated tumors, among others, that might have otherwise been impossible to treat.[76,104]

Conclusion

CBCT-based and MRI-based online ART have gained increasing adoption due to their ability to address daily anatomical variations that are difficult to account for with conventional RT. Given the significant efforts from manufacturers and leading academic centers to advance online ART, we anticipate broader adoption of online ART (potentially even real-time ART) in the near future. However, implementing these technologies remains costly and time-intensive. Therefore, a strategic approach for careful patient selection is essential to ensure that the selected patients could benefit most from online ART and that resources are effectively utilized.

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