See, Think, Act: Real-Time Adaptive Radiotherapy

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Abstract
The world is embracing the information age, with real-time data at hand to assist with many decisions. Similarly, in cancer radiotherapy we are inexorably moving towards using information in a smarter and faster fashion, to usher in the age of real-time adaptive radiotherapy. The three critical steps of real-time adaptive radiotherapy, aligned with driverless vehicle technology are a continuous see, think, act loop. See: use imaging systems to probe the patient anatomy or physiology as it evolves with time. Think: use current and prior information to optimize the treatment using the available adaptive degrees of freedom. Act: deliver the real-time adapted treatment. This paper expands upon these three critical steps for real-time adaptive radiotherapy, provides a historical context, reviews the clinical rationale and gives a future outlook for real-time adaptive radiotherapy.

Introduction to real-time adaptive radiotherapy using a real-world analogy, driverless car technology

Due to developments in sensors, processing power and artificial intelligence, driverless car technology is rapidly progressing motivated by the potential for dramatically improved safety. Reasons for the adoption of driverless technology include the staggering human and economic cost of road accidents, with 33,000 deaths and costing the US $871B in 2010,* likely significantly lower insurance costs and the consumer desire for safety for selves and loved ones. Replacing manual tasks with automated tasks frees the driver to perform productive tasks. Various industry sources estimate that the early 2020s will see the availability of multiple commercial driverless car options initially targeted at the higher end of the market with the tipping point of widespread adoption being in the mid-2030s.

In parallel with driverless car technology, real-time adaptive radiotherapy technology is rapidly progressing due to the potential for improved patient safety through measuring and correcting for anatomical changes during treatment, simultaneously enabling more accurate tumor targeting and smaller clinical target volume (CTV) to planning target volume (PTV) margins. Reasons for the adoption of real-time adaptive radiotherapy technology include reducing the human and economic costs of treatment-related side effects, improving local control, improving patient throughput and potentially using automation to reduce staff needs.

Driverless cars see their environment in real-time through an array of sensors. They think by using artificial intelligence to assimilate the real-time information regarding the nature and behavior of static and dynamic objects in their environment with prior knowledge to determine the best course of action. The initial plan to reach a destination is continually adjusted en route by adapting to changing traffic conditions, weather and identified risks. Driverless cars act by controlling two simple variables, direction and speed. The three steps of see, think and act have direct analogies to real-time adaptive radiotherapy. The systems see the patient using one or more sensors. They think by integrating the real-time patient sensing information with prior knowledge from the treatment plan and motion measurements to determine the best course of action. The plan to deliver the desired dose is continually adjusted by adapting to changing anatomy. Real-time adaptive radiotherapy systems act by controlling two simple variables, beam-target alignment and dose rate. The analogy

* https://www.pbs.org/newshour/nation/motor-vehicle-crashes-u-s-cost-871-billion-year-federal-study-finds

between the three common See, Think, Act tasks of driverless car technology and real-time adaptive radiotherapy is given in Figure 1.

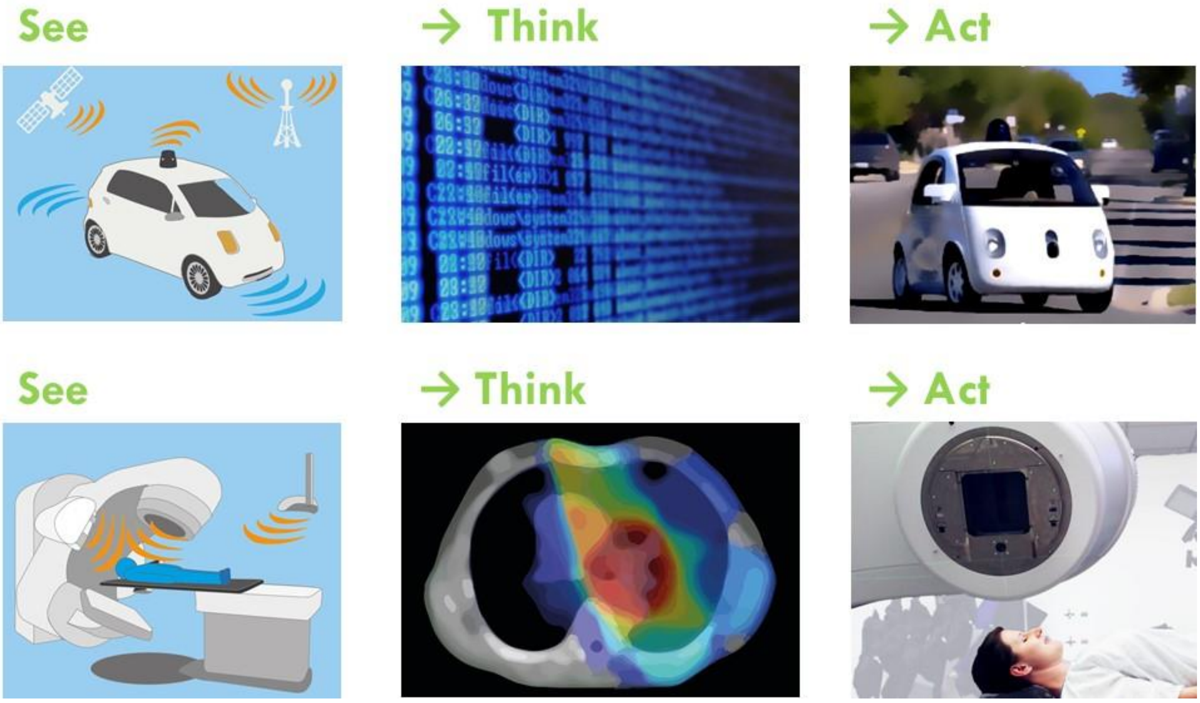

Figure 1. *Common stages of driverless car technology and real-time adaptive radiotherapy. See: multiple sensors are used to probe the environment. Think: current and prior information is rapidly processed to make decisions. Act: decisions are actuated by controlling only two variables: direction and magnitude.*

Rationale and clinical justification for real-time adaptive radiotherapy

In modern image guided radiotherapy, we image our patients prior to treatment. This information is useful, but the information is immediately old. The time we need to know the patient anatomy is during treatment, not prior to treatment. The respiratory, circulatory, digestive and muscular systems cause tumor motion on sub-second to minute timescales (Figure 2). Taking the respiratory system as one example, the magnitude and variability of patient measured tumor motion from day-to-day is exemplified by data from Shah *et al.*[39] Breathing induced motion varies from cycle to cycle – from a few millimeters to centimeters with cycle shape changes – and from day to day as shown in Figure 3. This variability in motion challenges any assumptions we have about patient motion from prior observations, as we cannot confidently predict the motion magnitude during treatment.

Figure 2. *The key driver for real-time adaptive radiotherapy is simply that tumors and normal tissue move during treatment. This motion challenges the tenet of radiotherapy to irradiate the tumor and reduce dose to normal tissues.*

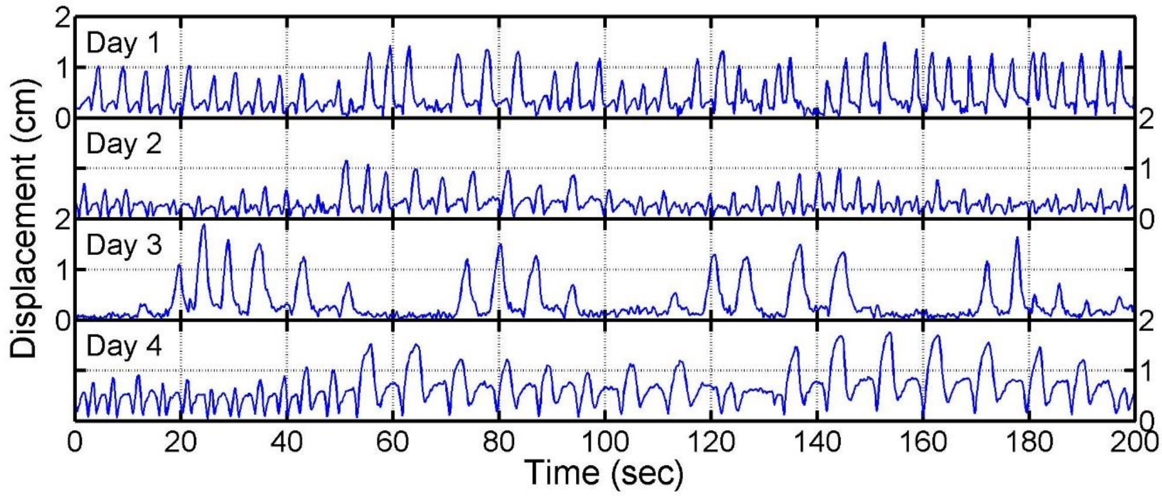

Figure 3. *Lung tumor motion measured on different treatment days showing the variability of cycle to cycle and day to day motion. Adapted from Shah et al.[39]*

An example of the dosimetric impact of digestive and/or muscular motion during prostate cancer radiotherapy, and the benefit of real-time adaptation, is given in Figure 4 (adapted from [21]). When there is unaccounted for motion during treatment, the target can be underdosed and the normal tissues overdosed.

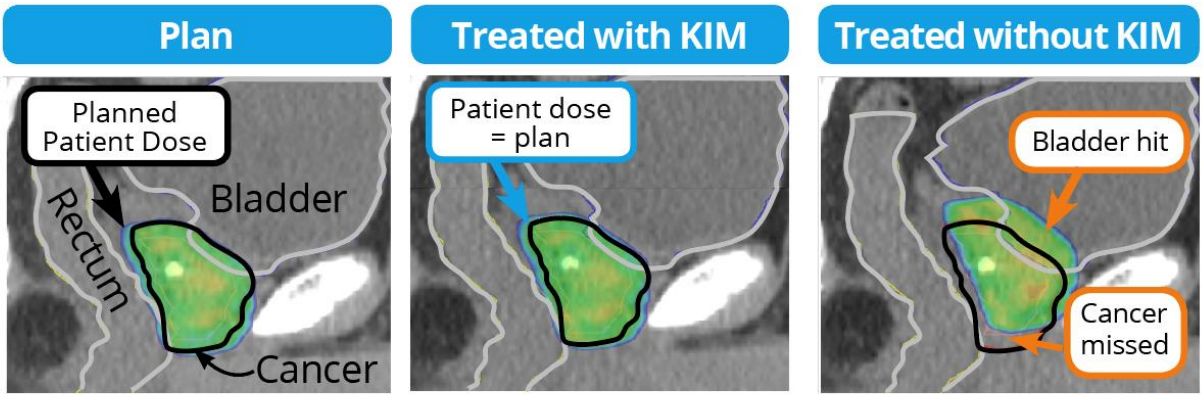

Figure 4. *The dosimetric impact of digestive and/or muscular motion during prostate cancer radiotherapy. The planned patient dose (left), dose with real-time adaptive radiotherapy (center) and the estimated dose without real-time adaptive radiotherapy (right) demonstrate that when there is motion that is not accounted for, the target is underdosed and normal tissues are overdosed. The color wash spans dose intervals of 95%-108%. Figure adapted from [21]. KIM = kilovoltage intrafraction monitoring, a real-time image guide method that was integrated with MLC tracking for this treatment.*

Real-time adaptation of radiotherapy treatment delivery increases targeting accuracy of moving lesions fundamentally improving safety and efficacy. With increased accuracy flows reduction of margins and subsequent reduction in collateral radiation exposure to nearby healthy tissue. Across all clinically implemented tracking systems, including robotic tracking [45], MLC tracking [6] and gimbal tracking [28], lung cancer margins are demonstrated to be reduced by up 50% providing mean lung dose decreases of up to 1Gy with the application of real-time adaptation. Lung toxicity exhibits a dose response relationship so that across a population, patients should benefit with lower toxicity while maintaining high tumor control [2]. A further benefit may extend to those patients in the oligometastatic setting, where any reduction in lung dose provides an opportunity for patients to access further radiotherapy if new lesions appear.

A corollary option available with real-time adaptation is advantageous in the setting of isotoxic prescriptions where reduction in uncertainty margins permit increased target dose (potentially tipping above a limit to tumoricidal doses) where otherwise not possible. A recent study has demonstrated such benefit for liver cancer, where an isotoxic prescription seeks target dose to exceed BED 100 Gy_{10} but can be limited by the volume of healthy liver sparing (<~13Gy) required to preserve liver function. Gargett *et al.* [13] planned 20 liver stereotactic cases with and without internal target volume (ITV) expansion and showed that of the 13 ITV plans that failed to meet both liver and tumor constraints, 11 plans met both constraints with the no-ITV plan. Recent daily adaptive planning studies for pancreas have also demonstrated superior patient outcomes, with Rudra *et al.* showing an increase of the number of patients able to receive BED > 70Gy and predicting for improved overall survival.[38] Daily adaptive treatment might be viewed as a subset of real-time adaptation where inter fractional changes are accounted for but not intra-fractional change.

With MR-linacs, PET-linacs and improved image registration at the point of care, both real-time geometry (location/shape) and radiobiological (functional imaging) are promising. For prostate cancer PSMA-PET[46] has drastically changed target volumes for radiotherapy and pushed towards smaller fields targeting intra-prostatic and metastatic nodules – requiring advanced planning techniques such as dose painting. Real-time adaptation has been demonstrated to meet the challenge of dose painting. MLC tracking accurately reproduced planned dose painted distributions under motion to tandem functional imaging [7]. With more frequent or intra-treatment imaging, functional response and imaging will be paired routinely in the presence of motion to maximize utility of radiotherapy with real-time adaptation. Such technology evolution may present new options, such as treating cardiac disease [24], or treating central lung lesions.

While real-time adaptation has been demonstrated for many years on specialist linear accelerators and with bountiful potential on MR-linacs; only relatively small clinical trials have been performed on standard-equipped linacs that are found in most clinics. Research continues into markerless tumor tracking and kV-based tracking to expand the patient cohorts with access to real-time adaptation.

Historical development of real-time adaptive radiotherapy

Some of the clinical milestones in the historical development of real-time adaptive radiotherapy are given in Table 1. It is important to acknowledge the pioneers of real-time adaptive radiotherapy: Tsukuba University who, over 30 years ago, first treated patients using respiratory gating by an external sensor[31] and Prof Shirato and his team at Hokkaido University who, over 20 years ago in 1998, first treated patients using respiratory gating by x-ray guided fiducial targeting.[41]

Table 1. *Selected clinical milestones in real-time adaptive radiotherapy.*

Publication year and reference	Guidance method	Beam-target adaptation method	Description
1989 [31]	Abdominal/thoracic pressure sensor	Automatic MV beam gating	First treatments with respiratory motion monitoring and gating (lung cancer)
1992 [15]	Strain gauge monitoring chest wall motion	Automatic proton beam gating	First particle therapy treatments with respiratory motion monitoring and gating (liver cancer)
1999 [41]	Room-mounted x-ray imagers, implanted markers	Automatic MV beam gating	First treatments with real-time image guidance (lung and liver cancer)
2000 [22]	Video camera	Automatic MV beam gating	Precursor to the widely available Real-Time Position Management (RPM) system (lung, pancreas, esophagus cancer)
2006 [43]	Electromagnetic guidance	MV beam gating	First treatments with the Calypso system (prostate cancer)
2008 [33]	Combined dual x-ray and infrared tracking	Robotic linear accelerator tracking	Early treatments on the CyberKnife linear accelerator using the Synchrony system (lung cancer)
2009 [5]	Combined dual x-ray and infrared tracking	Robotic linear accelerator tracking	Early treatments on the CyberKnife linear accelerator using the markerless XSight Lung system (lung cancer)
2013 [9]	Radioisotope	None	First clinical use of the Navotek RealEye system – now discontinued (prostate cancer)
2014 [25]	Combined dual x-ray and infrared tracking	Gimbaled linear accelerator tracking	Early treatments on the Vero linear accelerator (lung cancer)
2014 [40]	Room-mounted x-ray imagers	Automatic proton beam gating	Application of the real-time radiotherapy technology [41] to proton beam treatments (liver cancer)
2014 [19]	Electromagnetic guidance (Calypso)	Multileaf collimator tracking	First patient treatment with multileaf collimator tracking (prostate cancer)
2015 [32]	Integrated MRI-guidance	Automatic MV beam gating	First patients treated on the ViewRay MRI-guided system (multiple cancer sites)
2015 [20]	Gantry-mounted x-ray imager	Manual MV beam gating	First patient treatment using real-time image guidance using standard cancer radiotherapy equipment

			(prostate cancer)
2016 [27]	Room-mounted x-ray imagers	Automatic carbon ion gating	First patient treatments with markerless tumor tracking on a particle therapy system (lung and liver cancer)
2018 [18]	Gantry-mounted x-ray imager	Multileaf collimator tracking	Integrated real-time image guidance and beam-target alignment treatment using standard cancer radiotherapy equipment (prostate cancer)
?	?	Couch tracking	We anticipate the first patient treatment with the widely available treatment couch

See: Technology to Locate the Target During Real-time Adaptive Radiotherapy

Technologies to locate the target during real-time adaptive radiotherapy span many parts of the electromagnetic spectrum as shown in Figure 5. Technologies such as Calypso and RayPilot utilize radiofrequency waves [4,23,43] as do integrated MRI-radiotherapy systems [11,29,35]. There are several vendors for optical technology utilizing visible or near visible spectrum technologies. These surface or surface marker technologies can be combined with other imaging systems, e.g. x-rays, to give internal target positions at high temporal resolution with lower imaging doses than continuous x-ray imaging. Kilovoltage and megavoltage imaging systems utilize x-rays from dedicated x-ray tubes and the treatment beam itself, respectively. Gamma-rays have been used for real-time image guidance in the Navotek system (now discontinued). [9] Also shown in Figure 5 is an example of non-electromagnetic image guidance, the fast-developing ultrasound technology [1].

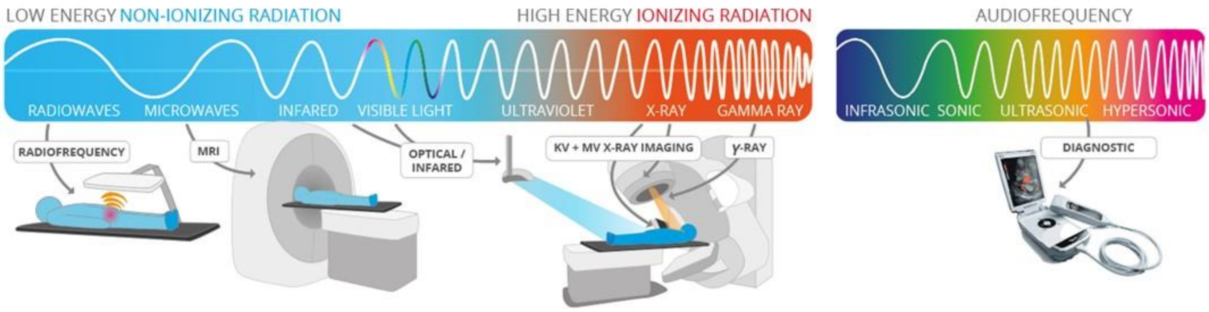

Figure 5. *Technologies to locate the target during real-time adaptive radiotherapy include a variety of frequencies of the electromagnetic spectrum and ultrasound.*

Think: Dose Calculation During Real-time Adaptive Radiotherapy

The current clinical state-of-the-art real-time adaptive radiotherapy corrects for changes in the target geometry only – essentially a first order correction to have the beam pointing at the moving target. This approach can be further improved by optimizing the quantity of interest – the delivered dose to the patient – in real-time to allow higher order corrections. A prerequisite for dose-guided real-time treatment adaptation is that the dose delivered to the moving anatomy can be estimated on-the-fly as the treatment progresses.

Sufficiently fast motion-including dose reconstruction for real-time application has so far been obtained either by relying on pre-calculated doses from a treatment planning system [12] or by reducing the dose calculation complexity to a minimum level [36]. Fast *et al.* [12] divided all treatment beams into beamlets and pre-calculated the dose distribution contributed by each possible beamlet in the patient anatomy. During treatment delivery, real-time motion-including dose reconstruction was obtained by assigning the pre-calculated doses at each dose increment calculation to different tissue elements depending on the current beam shape and target position. The use of pre-calculated doses gives flexibility to use more advanced dose algorithms at unaltered real-time speed, e.g. to include the impact of a magnetic field. Real-time dose reconstruction with this approach has been demonstrated during delivery of both prostate [12] [17] and lung plans [16] . No motion phantom or monitoring system were used in the experiments, but motion was simulated by real-time broadcasting of a pre-defined target position stream to the dose reconstruction software. For lung tumors, the dose reconstruction uses pre-calculated doses for each respiratory phase and deformation vector fields for deformable summation of the dose onto a reference phase [16].

Fast motion-inclusion dose reconstruction may alternatively be obtained by reducing the complexity to a minimum as proposed by Ravkilde *et al*. and implemented in their DoseTracker software [36,37]. A simplified pencil beam algorithm is applied that assumes homogeneous tissue density (typically water), flat patient surfaces, flat dose profiles and the same output factor and depth dose curve for all fields [37]. DoseTracker calculates both the actual motion-including dose and the planned static dose in a set of calculation points in real time. Comparison of the dynamic dose with the static dose provides the motion-induced dose error, which was shown to agree well with phantom dose measurements despite the simplified dose algorithm [37]. A main reason is that dose calculation errors present in both the dynamic and static dose tend to cancel out when the two doses are compared.

In patients, (offline) real-time dose reconstruction with DoseTracker for liver [42] and prostate plans [30] showed motion-induced reductions in the target dose coverage in good agreement with treatment planning system calculations [34]. An example for prostate cancer radiotherapy is shown in Figure 6.

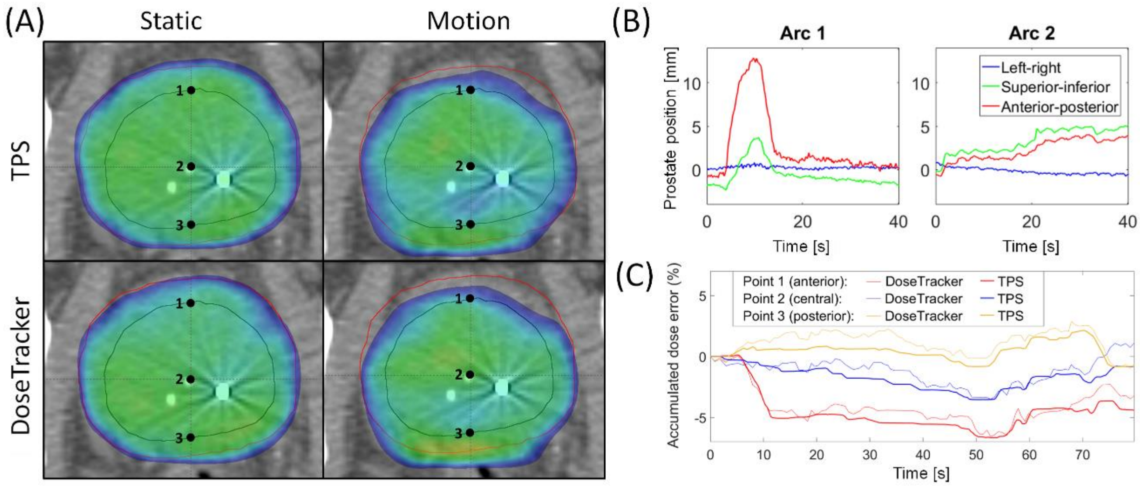

Figure 6. *(A) Prostate dose calculated by a treatment planning system (TPS) (top) and in real-time by DoseTracker during simulated delivery of a two-arc VMAT plan (bottom) without motion and with the prostate motion shown in (B). The dose colour wash range is 90-110%. The contours are the prostate (inner contour) and planning target volume (outer contour). The real-time reconstructed dose is in general in good agreement with the more accurate TPS dose calculation. (C) Accumulated dose error caused by the motion in the three points indicated in (A) as calculated by DoseTracker (thin curves) and the TPS (thick). The transient anterior prostate excursion after 5-10 seconds (see (B)) gives a 5% dose deficit in Point 1. Adapted from [40].*

Act: Technology to Hit the Target During Real-time Adaptive Radiotherapy

Once the anatomic changes are seen, the adaptive thinking process complete, action is needed to complete the real-time adaptive radiotherapy loop. The earliest implementation of adaptive radiotherapy, as described in Table 1, is gating the treatment beam off when the target (or a surrogate for the target position) is outside a pre-specified range. [31] Gating can be applied for respiratory motion, e.g. only turning the beam on during the exhale phase of breathing, or other motion, e.g. pausing the beam if prostate motion from the isocenter exceeds a given threshold. The advantages of gating are the ease of use and widespread applicability. The limitations of gating are the commensurate decrease in efficiency whilst the beam is off, and the residual motion of the target within the gating limits. The smaller the gating limits, the lower the residual motion but the efficiency is decreased. Conversely, the higher the gating limits, the more residual motion but the efficiency is increased. Image-based gating has been implemented for motion management on the ViewRay system. [32]

To overcome the tradeoff between efficiency and residual motion, ideally gating is combined with a method to continuously realign the beam and the moving target. Four technologies to hit the target during real-time adaptive radiotherapy are shown in Figure 7.

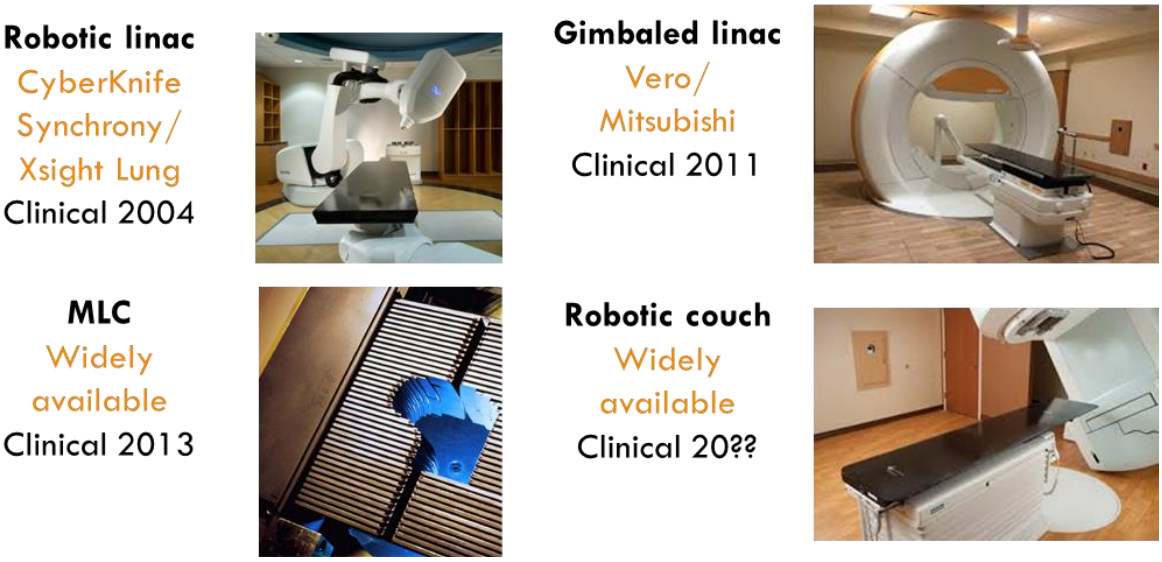

Figure 7. *Technologies to hit the target during real-time adaptive radiotherapy include robotic, gimbaled, multileaf collimator and couch tracking systems.*

The pioneering technology of continuously realigning the beam and the moving target was introduced with the Synchrony method on the CyberKnife linear accelerator (e.g. [33]). The Synchrony method combines near-continuous surface position monitoring with occasional dual-source x-ray imaging to determine the target position in real-time. The beam-target correction is performed using a widely available technology for many complex and precise industrial applications – a robot. Time delays are accounted for using a motion prediction algorithm. The second technology used to continuously realign the beam and the moving target is the gimbaled linac, a novel technology where motors enabled the linac to rotate in two directions (pan and tilt), thus allowing the beam to follow the target (e.g. [25]). Near-continuous surface position monitoring with occasional dual-source x-ray imaging is used to determine the target position in real-time which is fed to the gimbaled linac to actuate motion. Unfortunately, the production of the gimbaled linac has been discontinued. The third technology used to continuously realign the beam and the moving target is the multileaf collimator (MLC), a widely available beam shaping tool (e.g. [19]). The MLC is the smallest and lightest of the four adaptation systems, and in addition to correcting for targeting translational motion, non-clinical experiments have also demonstrated the ability to correct for real-time target rotation [44] and deformation either of a single target or a dual target system moving with differential motion.[14] The fourth technology used to continuously realign the beam and the moving target – though not yet clinically implemented – is the robotic couch. Similarly, with the MLC, the couch is widely available and could be broadly implemented to correct for translational target motion. Several experimental implementations of couch tracking have been performed, (e.g. [8,10,26]) and we look forward to the first clinical implementation of this technology. Note that of the four technologies described in Figure 7 for photon beam therapy, couch tracking is applicable to particle beam therapy. Gating has been clinically implemented for particle therapy [15] and real-time particle beam steering has been demonstrated in phantoms [3].

Future outlook

The future outlook for real-time adaptive radiotherapy, like driverless car technology is obvious – routine implementation with massive savings in efficiency and quality. What is uncertain is the timeframe for implementation. Efficiency will be dramatically improved by omitting the time-consuming process of careful patient setup, alignment and realignment. A shorter treatment time improves the patient experience of radiotherapy and reduces the economic cost of delivering radiotherapy. Improved treatment accuracy can also further enable hypofractionated radiotherapy, improving the patient experience and delivery costs. Quality will be improved not only by meeting the goal of radiotherapy, to hit the tumor with the radiation beam, but also through machine learning continually assessing all aspects of the patient's treatment, including target and normal tissue contours, time/dose/fractionation, disease changes, comorbidities, genetics, liquid biopsies etc. to further personalize care and maximize outcomes for each patient. The individual patient data will be combined with population data mined from thousands of scientific articles to benefit the current patient and in turn, use the information learned from the treatment to benefit future patients.

Summary

Motion management technology to account for real-time changes in anatomy has been clinically applied for over 30 years. Steadily increasing progress has been made towards the widespread implementation of real-time adaptive radiotherapy. Future challenges, aligned with technological development and economic drivers, are to use automation to make cancer radiotherapy treatments fast, efficient and accurate. Manufacturers, researchers, government and consumers are urged to work together to realize the future of real-time adaptive radiotherapy.

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Conflicts of interest

This review article spans many clinically available and under development technologies related to real-time adaptive radiotherapy. To ensure full disclosure of conflicts for PJK these are publicly available at http://sydney.edu.au/medicine/image-x/about/disclosures.php.

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