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Adaptive Radiotherapy Enabled by MRI Guidance

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Abstract

Adaptive radiotherapy (ART) strategies systematically monitor variations in target and neighbouring structures to inform treatment-plan modification during radiotherapy. This is necessary because a single plan designed before treatment is insufficient to capture the actual dose delivered to the target and adjacent critical structures during the course of radiotherapy. Magnetic resonance imaging (MRI) provides superior soft-tissue image contrast over current standard X-ray-based technologies without additional radiation exposure. With integrated MRI and radiotherapy platforms permitting motion monitoring during treatment delivery, it is possible that adaption can be informed by real-time anatomical imaging. This allows greater treatment accuracy in terms of dose delivered to target with smaller, individualised treatment margins. The use of functional MRI sequences would permit ART to be informed by imaging biomarkers, so allowing both personalised geometric and biological adaption. In this review, we discuss ART solutions enabled by MRI guidance and its potential gains for our patients across tumour types.

Key words: Adaptive radiotherapy; gating; image guided; magnetic resonance imaging; radiotherapy planning; tracking

Search Strategy and Selection Criteria

An electronic literature search was carried out using PubMed and Web of Science databases. The final search was carried out in July 2018. Search terms included “radiotherapy”, “radiotherapy planning”, “adaptive radiotherapy”, “online adaptive radiotherapy”, “magnetic resonance”, “MR”, “MR-guided”, “radiotherapy tracking”, and “radiotherapy gating”. The search was restricted to those published in English with preference given to more recent studies. Selected studies were first screened by their title and/or abstract followed by full article review of relevant articles. A manual review of the reference list of relevant studies was also undertaken.

Introduction

The target for radiotherapy is dynamic. It varies in position, shape, size, and biology over a time frame that extends over seconds, days, and weeks (Figure 1). Reliance on a single pre-treatment planning computed tomography (CT) scan to capture this change over the treatment course is misplaced. Historically, to try and account for this geometric variation, large margins have been used to create the planning target volume (PTV) [1–3]. This, however, often limits dose escalation to tumoricidal levels because of concerns regarding collateral damage to adjacent normal structures [4,5].

Accepting that the PTV is a statistical construct to ensure that dose can be successfully delivered to the tumour, reliably decreasing PTV size is only possible when there is confidence in target positioning during treatment. Technologies that have enabled imaging in the treatment room have allowed gains to be made on this front, so overcoming, in part, the challenge of hitting an otherwise invisible target with an invisible beam. Image-guided radiotherapies (IGRTs), particularly those permitting soft-tissue visualisation, such as cone-beam CT (CBCT), prior to treatment delivery, have already demonstrated step-wise improvement in target coverage. This has been achieved using smaller margins and a subsequent reduction in integral

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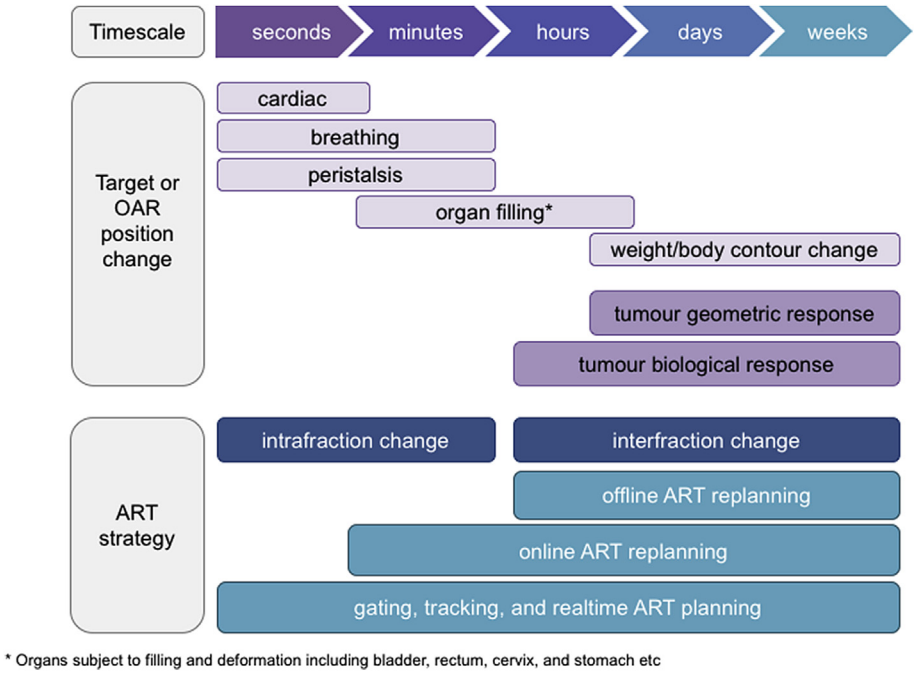

Fig 1. Timescales for adaptation and ART solutions implemented .

dose to surrounding tissues when compared to surrogates for target position such as skin tattoos or bony anatomy [6].

Adaptive radiotherapy (ART) is an umbrella term encompassing techniques that allow knowledge of patient-specific anatomical variations informed by IGRT to feedback into the plan and dose-delivery optimisation during the treatment course [7]. This ensures that the planned dose is delivered as accurately and precisely as possible according to the anatomy of the day. ART can be implemented broadly over three timescales (Figure 1): (1) offline between fractions, (2) online immediately prior to a fraction, and (3) in real-time during a fraction.

Offline ART monitors the position of the target during a limited number of fractions. It addresses systematic changes to some extent, but also allows opportunity for an individualised PTV margin to be applied based on acquired knowledge of the location of volumes of interest and patient set-up. Although adaptation is not informed by the exact position of the tumour at each fraction, the applied margins are often smaller than population derived margin recipes [8,9]. Online and real-time ART protocols modify the treatment plan while the patient remains on the couch. These strategies allow for a patient specific PTV to be created because they are informed by the actual change in anatomy seen for that fraction. As there is greater certainty to the true position of the tumour, an even smaller “safety” margin can be considered. The confidence in soft-tissue targeting at the time of radiotherapy delivery provides an opportunity to deliver higher radiation doses with tighter margins. In this review, we discuss ART solutions enabled by magnetic resonance imaging (MRI) guidance and it potential gains for our patients.

Will MRI-Guided Radiotherapy be the Ultimate Online IGRT Solution?

The persisting weakest link in the treatment chain for radiotherapy remains clinician-led target identification [10,11]. Repeated studies have demonstrated that gross tumour volume (GTV) and organ at risk (OARs) delineation variability between observers introduces systematic errors, which are larger than daily set-up uncertainties [12–14].

One of the most important factors responsible for the observed target variation is adequate imaging [12]. Compared to CT or CBCT, MRI offers superior soft-tissue definition with no associated radiation risk [15–17]. As a result, for many tumours diagnostic MRI improves inter- and intra-observer delineation consistency [12,18–20]. Observer variation also improves with the use of standardised guidelines, anatomy atlases, and auto-segmentation tools [21].

MRI delineated target volumes are often reported to be significantly different from those contoured on CT. Occasionally, MRI identifies targets larger than on CT because tumour that otherwise would have been missed is now seen [20]; however, most commonly, targets are reported to be smaller when delineated on MRI [18,19,22,23]. The resulting smaller MRI-derived target improves the therapeutic ratio so enabling dose escalation. For example, an MRI-delineated prostate, allows dose escalation of 2–7 Gy while maintaining the same rectal wall dose compared with a CT-delineated prostate [24]. Similarly, in cervical cancer, dose escalation is possible using an MRI-informed target with an associated 10–20% survival gain seen at 3 years with reduced gastrointestinal and urinary late morbidity [25].

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It is likely that MRI-guided IGRT will help define the 'right' radiotherapy target, but robust pathological correlation is necessary as the GTV is a factual construct of macroscopic disease. Only with this information will it be possible to know how closely the MRI visualised target represents the 'true' pathological target and how closely the delineated GTV represents actual disease [2]. Without this knowledge, although ART targets may get progressively smaller, and dose more conformal, we risk possible increases in marginal recurrences, undoing all efforts invested in improving radiotherapy precision and accuracy with this technology [26,27].

The availability of on-board 'functional' MRI sequences holds promise that geometric adaptation maybe complemented by biological adaptation. For example, diffusion-weighted imaging (DWI) is a functional imaging technique dependent on the inhibitory effect of cell membranes to the random motion of water molecules to generate image contrast. As tumours usually have greater cellularity than normal tissue, they demonstrate higher signal intensity, i.e., restricted diffusion on MRI. This is reflected in the low mean apparent diffusion coefficient (ADC) value. This has potential to provide both qualitative and quantitative information. Change in the ADC has been used to identify early treatment response, and to predict local recurrence [28–30]. Therefore, on-board DWI could identify early non-responders who may benefit from change in treatment approach [31].

The feasibility of biological ART based on functional imaging signal change mid-treatment has been shown possible in a single-arm Phase 2 study [32]. Kong *et al.*, used 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron-emission tomography CT (FDG-PET CT) mid-treatment to inform the volume for dose escalation (up to 80 Gy in 30 factions) in patients with inoperable stage II–III non-small cell lung cancer [32]. Similarly, DWI signal change during radiotherapy could be used to inform adaptation and dose escalation in relevant tumours [29]. Randomised control studies would be necessary to ensure no adverse impact on disease control occurred, as the shrinking metabolic target might inadvertently reduce coverage of macroscopic or microscopic disease [27].

The challenges of MRI acquisition and planning using an integrated MRI radiotherapy platform have been addressed in the accompanying articles in this special edition.

ART Techniques

Offline ART Solutions

Offline ART aims to correct for the systematic changes to either the target or OARs identified by in-room imaging during the course of treatment. Plan modification, however, takes place offline often adopting the same workflow as the original plan creation including repeat simulation. This is currently the commonest approach to accommodate changes that cannot be corrected by couch shift alone [8,9]. It is most often encountered when changes in patient contour are seen on CBCT because of weight change or treatment response during conventionally fractioned courses. These changes trigger the creation of a new plan in an attempt to improve dosimetry and achieve the planned prescription for the remaining fractions [33]. Until recently, this would have required a similar amount of time as generating the original plan, so limiting the frequency of adaption but developments in automated contour propagation and automatic plan re-optimisation open the possibility of more frequent plan adjustments [34,35].

When online image guidance informs offline adaptation, authors occasionally refer to this approach as 'hybrid adaptation' [17,36]. Hybrid and offline ART protocols offer the opportunity for patients to benefit from ART enabled by MRI guidance without an integrated MRI radiotherapy system using either a diagnostic MRI scanner, MRI simulator, or a shuttle-based MRI-guided radiotherapy system (MRI on rails) [37,38].

Although no consensus regarding the threshold to trigger offline ART exists, planning studies repeatedly show that a static patient model created at simulation is often obsolete and non-representative of the treatment course. Any adaption, even if implemented at a single time point during a conventionally fractionated treatment course, delivers dosimetric improvement above a single planning scan [33]. Oh *et al.*, showed that weekly online MRI with offline intensity-modulated radiotherapy (IMRT) re-planning using a 3 mm PTV margin in cervical cancer patients accounts for intrafraction pelvic organ motion and tumour shrinkage with measurably improved target coverage when compared to no or a single re-plan [17].

In many tumour types, daily imaging offers an advantage [39–41]. Decreasing the image frequency potentially increases the proportion of fractions associated with significant localisation errors. For example, in prostate cancer radiotherapy, decreasing the imaging frequency from daily to alternate day imaging, results in step up errors of >5 mm in 24% of fractions, which increases to approximately 40% when the set-up error threshold is >3 mm [39].

The logistics of repeated MRI outside the treatment room could be challenging; however, the feasibility for an offline ART protocol, informed by daily out-of-room MRI guidance has been shown to be possible using a shuttle-based MRI workflow in pelvic malignancies [38]. Median total treatment time for each fraction, including time for patient positioning, MRI acquisition, shuttle transfer to treatment suite, patient repositioning, CBCT acquisition, and IMRT delivery was over 1 hour (61 minutes; range 47–99 minutes) [38].

Symptomatic patients are unlikely to tolerate prolonged immobilisation very well. They are also more likely to have larger positional inaccuracies between out-of-room MRI and radiotherapy [38]. The long gap between MRI and treatment also means intrafractional organ motion uncertainties persist [13]. So, although offline/hybrid approaches may help bridge demands for MRI-enabled ART, alternative ART approaches are necessary to address both inter- and intrafraction motion.

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Online ART Solutions

Online Adaptive Re-planning

Online adaptive re-planning necessitates a rapid workflow that brings together online imaging, image registration, contour propagation, plan re-optimisation, quality assurance, and treatment delivery all while the patient is on the treatment couch (Figure 2) [42].

Monte Carlo dose calculations are recognised as being the most accurate method for radiotherapy treatment planning, but until recently they had been constrained by long computational times precluding their use for rapid dose calculation. Proposed ways to accelerate Monte Carlo dose calculations are with graphical processing unit (GPU) technology, clusters of central processing units (CPUs), or cloud-based solutions [43–45]. Monte Carlo-based treatment planning systems are also needed to reliably model dose for any integrated MRI radiotherapy platform where the beam passes through the magnetic field. This is necessary because when the magnetic field is orthogonal to the radiation beam, the trajectories of secondary electrons are altered owing to the Lorentz force, resulting in high dose deposition at air-tissue interfaces, and so altering beam profiles than would otherwise be expected [46,47].

In its simplest forms online adaptation involves patient repositioning by shifting the plan to the relative anatomy seen on the day. This can be achieved by a simple couch shift to accommodate the interfraction change with no additional optimisation of the initial treatment plan [48,49]. This strategy provides only first-order correction, as target rotations, volume and shape change, and the geometric relationship to surrounding normal structures are not fully considered [50]. It is arguably more consistent with the definition of IGRT than ART, given that no plan revision takes place as a result of the acquired imaging [27]. An alternative online partial compensation for translational and rotational anatomy change involves adjusting pre-treatment gantry and collimator angles [51,52].

'Plan of the day' solution accesses a library of pre-prepared plans selected for treatment according to best anatomical fit for that fraction [53–56]. Although no further re-optimisation occurs, target size, position, deformation, and geometric relationship to adjacent structures are considered in part for the library creation [57]. For example, 'plan of the day' for cervical cancer radiotherapy utilises bladder filling to generate a model predicted ITV that is then used to inform the library creation [54].

'Virtual couch shift' or 'dose shift' approach translates and rotates the pre-treatment dose distribution (without new contour regeneration) to compensate for the positional changes in patient's anatomy. An alternative plan is automatically generated and delivered, producing a clinically similar dose distribution to pre-treatment, but at the new position [58]. This dose shift strategy is independent of any couch limitations and is therefore an important solution for the MRI-linear accelerator (linac) (Elekta AB, Stockholm, Sweden), which at present does not allow table shifts [59].

Use of a deformation field has also provided a solution for a number of other online adaptive re-planning strategies [60–62]. The method is essentially reliant on deriving a three-dimensional (3D) geometrical transformational matrix from the planning scan and the image of the day, and using it to 'morph' the treatment plan as an online correction method. An alternative approach is to perform online ART based on a new target outline [50]. A number of single centres have successfully implemented online ART re-planning workflows, demonstrating both feasibility and dosimetric benefit of this approach [42,60,63,64].

Acharya *et al.* utilising the MRIdian platform (ViewRay Inc., Oakwood Village, OH, USA) illustrate clinical feasibility of treating abdominal malignancies with gated motion management and conventional fractionation. An online re-optimisation trigger was based on maintaining pre-determined target and OARs dose–volume histogram (DVH) constraints when the initial plan to anatomy of the day was fused. If the PTV dose was inadequate or the critical structure dose was exceeded, re-optimisation was performed on the anatomy of the day. Using this criterion, 30.6% (52/170) fractions were treated with online re-optimisation and 54.1% (92/170) fractions were treated with either an online adapted plan or previously adapted plan [42].

In a prospective Phase I study, stereotactic MRI-guided online ART was used to treat primary abdominal tumours. Initial plan performance was evaluated on the MRI 'anatomy of the day'. Using this approach, 84% (81/97) fractions were treated with online adaptation. Although the majority of fractions (63%; 61/97) necessitated adaptation because OARs DVH constraints would have been violated if the initial plan had been used, in 21% (20/97) of fractions anatomy of the day appeared favourable for dose escalation while maintaining strict OAR constraints [65].

For primary abdominal malignancies, such as locally advanced pancreatic cancer, the ability to dose escalate has the potential to improve clinical outcomes [66]. Without online MRI informed re-optimisation, radiation dose has been limited to sub-ablative levels because of poor visualisation of OARs and normal tissue toxicity [67].

Simulation studies reflect that daily online adaptation would also provide a dosimetric advantage at other

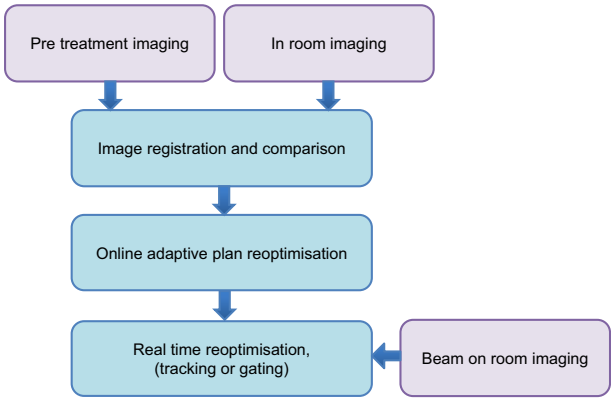

Fig 2. Typical workflow of ART.

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anatomical sites. For example, in the pelvis, daily re-optimisation in bladder cancer radiotherapy based on anatomy of the day is superior to both PTV with population derived margins, i.e., no adaptation, and to 'plan of the day' approach. This is achieved with a decrease in PTV size and subsequent reduction in normal bowel irradiation [40]. Similarly, in cervical cancer, online re-planning using MRI guidance reduces the absolute volume of small bowel receiving more than 45 Gy (V45Gy) by approximately 100 cm^3 [68].

Advanced Motion Management: Gating

Any effective ART strategy is reliant on its ability to acquire high-quality online images with high geometric and temporal resolution [69,70]. The greater the delay between imaging and treatment, the greater the opportunities for short-term organ motion [13]. Integrated MRI-guided platforms enable rapid high-quality imaging to take place immediately before and during the delivery of each radiotherapy fraction. This 'beam-on' imaging means motion monitoring occurs during treatment delivery and is able to provide opportunity for 'real-time' anatomical feedback to inform adaptation. Motion blurring is reduced by speed of MRI data acquisition.

Intrafractional motion varies according to tumour position within the body [71,72]. Breathing motion can result in target lesions in the lung or intra-abdominal cavity moving several millimetres or several centimetres [73,74]. To try and capture tumour motion throughout the breathing cycle, four-dimensional (4D) CT has been used to inform a personalised internal target volume (ITV). Breathing motion, however, is often unpredictable, and single 4D CT is rarely representative of true range of motion through treatment and so requires application of large treatment margins to avoid geographical miss [75–77].

Gating mitigates intrafractional motion by delivering dose only when target is within a defined geographical position. By convention, position recognition for gating has been reliant on either being able to see the target on CBCT, the use of external surrogates [78], implanted radiopaque markers [79] or electromagnetic transponders [80]. These methods successfully improve geometric and dosimetric accuracy compared to non-gated approaches [81].

An MRI-gated solution provides adequate visualisation of the target and therefore can be performed without implanted devices or potentially unreliable external surrogates [82]. Gating without implanted devices or external surrogates is currently in use within the MRIdian system (ViewRay Inc.). Using this approach the GTV to PTV margin has been reduced from 5 to 2 mm for stereotactic ablative radiotherapy [63].

Advanced Motion Management: Tracking

Tracking is a technique whereby the target is 'followed' by the radiation beam, and treatment delivery parameters are continually adjusted to compensate for tumour motion. The target remains within the beams eye view at all times. Unlike gating, the treatment machine is always on and so treatment times are expected to be comparably shorter [83].

Tracking can be achieved in one of three ways: it is possible to shift the treatment source to track tumour motion, to shift the beam using multi-leaf collimators (MLCs), or adjust the patient position relative to the stationary beam [84]. Robotic, gimballed, MLC, and couch-tracking systems are all solutions implemented for tumour tracking [84–86]. They rely on CT and kilovoltage image guidance or implanted devices.

MRI-guided tracking is possible because the superior soft-tissue definition allows easy identification of target and OARs deformation and rotation [87]. This is advantageous because surrogates for tumour position have limitations in their ability to accurately describe motion [88–90].

In a proof of concept study, it has been possible to track motion using MLCs in combination with a fast one-dimensional (1D) MRI sequence [83]. An MRI-guided two-dimensional (2D) tracking solution has also been determined [90]. Although MRI-informed tracking is not yet in clinical practice, it is expected to be possible soon. Simulation work in lung cancer cases suggests when clinically implemented, it would be expected to spare healthy tissue, including reducing the mean lung, skin, and great vessels dose while maintaining dose to 98% of GTV compared to conventional dose deliveries [91]. The reported improvements in normal tissue irradiation reflect ability to deliver treatment using tracking on a gantry-based linac with reduced PTV size compared to the standard ITV approach. If this technique were to be applied for the treatment of lung and pancreatic cancer, the PTV could be reduced by up to 40% and 17%, respectively [92,93].

Real-Time Adaptive Re-planning

Real-time ART has the potential to improve accuracy of the delivered dose to target with normal tissue sparing, independent of the delivery system [84]. This suggests that each fraction should be adapted irrespective of predetermined action levels. Adapting the plan during beam delivery necessitates continuous imaging with a real-time motion management method, re-planning, and rapid dose calculation.

The team from the University Medical Centre Utrecht recently published a potential solution to this problem illustrated in a proof of principle study based on their Elekta MR-linac (Elekta AB, Stockholm, Sweden). This study describes a novel real-time adaptive treatment pathway where intrafraction, inter-beam re-planning and optimisation takes place, taking into account the previously delivered dose within that fraction accumulated onto the underlying moving anatomy [94].

Fast inverse IMRT re-planning based on the updated 3D anatomy during intrafraction delivery was possible in part because of a treatment planning method called adaptive sequencer (ASEQ) [95]. ASEQ is an iterative process that begins with initial optimisation that faithfully reflects the ideal/prescribed dose. Each iteration produces unique

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segments that follow the anatomy seen. The dose of that segment is calculated and is subtracted from the ideal dose distribution. The updated dose distribution then informs the next iteration. This is repeated until dose convergence between the delivered and prescribed dose occurs [95,96].

In the context of a single fraction (25 Gy) stereotactic body radiotherapy (SBRT) planning study, application of ASEQ showed that inter-beam IMRT re-planning to a no-margin PTV had theoretical benefit with higher dose target coverage, tighter dose distributions, and improved normal tissue sparing compared to a mid-respiratory position SBRT plan with a 3 mm PTV margin. The high dose region (defined as 2 cm around the target) was decreased by an average of 27.8% with real-time planning [94]. A no-margin PTV was only feasible because MRI data were continuously informing the 3D anatomical deformations of the target and OARs during treatment delivery [94].

Future Considerations for MRI-Guided ART

It is attractive to envision that we are entering a new era of radiotherapy. MRI-guided ART enabled by technological and computational advances has increased the precision of RT with potential increase in the therapeutic window. We would, however, advocate caution, as we are yet to demonstrate that the dosimetric gains seen will translate to meaningful clinical outcomes for our patients [97].

It is certain that not all patients will derive the same benefit with ART. Prospective evaluation within a robust framework is necessary [98,99]. Well-designed clinical trials remain the optimal method to evaluate patient benefit of this technology; however, head-to-head comparative studies of CT-guided and MRI-guided ART using standard dose and fractionations delivered to an anatomical target may not be ambitious enough to demonstrate the true potential of MRI-guided technology in terms of improved toxicity, local control, and survival. Many groups are investigating how MRI-guided ART provides a platform to deliver radiation in circumstances that would have otherwise been impossible. These include ultra-hypofractionation (single radical fraction) in regions of organ motion [100], safer re-irradiation [101], and integrating on-board functional MRI sequences to inform biological feedback for personalised adaptation [102]. The future of ART will be MRI guided, but how we choose to best apply this tool in order for it to be measurably transformative for patient outcomes remains to be determined.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clon.2018.08.001.

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