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Editorial

The Future of Image-guided Radiotherapy

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Dose-escalated radiotherapy using increasingly conformal techniques from three-dimensional conformal radiotherapy to step-and-shoot intensity-modulated radiotherapy (IMRT) through to volumetric-modulated arc therapy (VMAT) has been shown to improve outcomes in a number of different solid tumours [1–5]. This has been achieved while minimising the potential toxicity to surrounding normal tissue. However, the accuracy of radiotherapy delivery is limited by volume delineation, set-up error and intra-/inter-fraction organ deformation, motion and rotation. These uncertainties are reduced using optimal planning and image-guided radiotherapy (IGRT). The use of cone-beam computed tomography (CBCT) has improved the precision of radiotherapy, enabled the safe delivery of stereotactic ablative body radiotherapy and can produce results comparable with surgery [6]. Despite the successive incremental improvements in radiotherapy, the limitation of CBCT is that there is loss of image quality compared with the planning scan and it is suboptimal for many tissues [7].

Magnetic resonance imaging (MRI) provides improved soft-tissue contrast in many parts of the body and offers far superior in-room imaging for radiotherapy. Although other MRI guidance technology exists [8], at present only the MR-linear accelerator (MR-linac) is available in the UK. The MR-linac combines a 1.5T magnet with a linac. This allows diagnostic quality images to be taken during radiotherapy treatment with the potential for real-time adaptive planning and delivery. University Medical Centre Utrecht developed the prototype [9,10] with further advances made in collaboration with commercial partners, Elekta AB and Philips. The international MR-linac Consortium was formed in 2012 to introduce this new technology on a background of collaboration, research and robust evidence of clinical benefit. The consortium includes Elekta AB (Sweden), Philips (The Netherlands), University Medical Center Utrecht (The Netherlands), Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital (The Netherlands), The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust (UK), The Christie NHS Foundation Trust/Manchester Cancer Research Centre (UK), The University of Texas MD Anderson Cancer Center (USA), The Froedtert & Medical College Wisconsin (USA) and Sunnybrook Odette Cancer Center (Canada) [11]. With two of the consortium members in the UK, the era of MR-guided radiotherapy is fast approaching, although there are significant challenges ahead.

Physics Challenges

MRI and the linac are two machines that would initially appear to be antagonistic. The highly controlled magnetic fields of the MRI should interfere with the complex electronics and be disturbed by the shielding in the linac. However, with careful control of the magnetic field, a zero field area has been created for the linac and by placing the accelerator outside the Faraday cage the two machines are essentially isolated [9], therefore allowing the two to exist in the same room and to be used simultaneously.

The magnetic field interacts with dose deposition. Photons have a neutral charge and are unaffected by a magnetic field. However, the negatively charged secondary electrons undergo a trajectory change. The Atlantic system has a transverse magnetic field (through the bore). Therefore the electrons spiral around these field lines. This is the Lorentz force, otherwise named the electron return effect [12]. Essentially, in a patient the distance between interactions is

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small and no effect is seen. However, on exiting a patient or entering an air cavity inside a patient, the distance is great enough for the electrons to spiral and be incident on their exit point. This results in an increased dose deposited at these interfaces, possibly up to 30%. Planning studies have shown that this would result in clinically unacceptable plans for tangent pairs, for example standard breast plans [13]. However, for IMRT or VMAT deliveries, the multiple, non-opposing beam angles and modulation can compensate for this effect [14].

This effect is also present in machine calibration, where the magnetic field changes the response of the chamber. Additionally, the electron return effect, due to small air gaps around the calibration chamber itself, can cause uncertainty in the output measurement. Combined, these can introduce an uncertainty of up to 3%, greater than the acceptable range for clinical use of the machine. Work is underway to identify the most stable chambers in a magnetic field and to create phantoms to minimise these effects [15]. Quality control of the machine has to consider the MRI to radiation isocentre coincidence. The most suitable phantom for this work would identify the isocentre on both MR and MV imaging via the incorporated portal imaging device. All physics equipment used in this environment must be MR safe, or at least MR compatible.

The MR-linac promises a true online adaptive approach where plans can be optimised to the daily anatomy at each fraction. Simultaneous imaging will monitor the anatomy, terminating delivery if the dose to normal tissues exceeds tolerances or the target moves outside the planning target volume. Simultaneous imaging can also provide a more accurate calculation of the dose delivered to the moving anatomy. Such workflows may appear outlandish with our current techniques, but work is progressing to make this a reality. Adapting plans on daily anatomy will require fast optimisation in the planning system. In most cases, a patient's anatomy will not change significantly. Therefore, a minor adjustment should be sufficient. Segment aperture morphing algorithms have been developed that can accomplish this quickly and efficiently [16].

We also need means of propagating contours longitudinally through the patient's images. This will allow plan optimisation and review to take place. Currently, contours must be inspected directly, but for an online workflow this needs automated quality control. Such a test would flag contours for manual intervention. These workflows are being devised for clinical implementation [17]. The online adapted plan must also be deliverable, with the patient's prescription moving away from a simple dose and fractionation to incorporate information on allowed deviations from the accepted reference plan on a per-fraction basis.

Effective use of the MR-linac requires specific MRI sequences for IGRT. IGRT requires high geometric fidelity and with no artefacts that could obscure or deform patient anatomy. Fast sequences are required for tumour motion tracking and to reduce the time in the treatment position. Some sites are difficult to image with MRI. This is especially challenging in the lung, where respiratory and cardiac motion degrade image quality [18]. By overcoming these challenges we hope the MR-linac will achieve better soft-tissue contrast and nodal distinction during treatment.

Clinical Challenges

Technological advances contribute to the rising expense of healthcare. The evaluation of complex new technologies is difficult and inadequate [19,20], resulting in potentially costly and unnecessary use. One of the aims of the consortium is to introduce MR-guided radiotherapy with a clinical evidence base through a consolidated prospective registry alongside clinical trials. If a consolidated prospective registry is to be successful then standardisation of treatment is essential. One notable challenge in designing common trial protocols across two different continents is harmonising clinical practice. For example, within the prostate group there has been much discussion regarding the optimal dose and fractionation, even in light of the CHHiP trial [21].

The use of MRI is not standard practice for treatment planning in most tumour sites. Integration of MRI requires development of patient pathways, an appropriate skill mix for staff and initial dependence on specialities such as radiology. There are innate workflow challenges with such combined technology. The incorporation of MR with a linac requires the safety aspects of both linacs and MR machines to be incorporated in the bunkers with all immobilisation to be MR-compatible.

New technologies have often been introduced with little evidence. For example, the justification of IMRT for toxicity reduction in head and neck radiotherapy came from the PARSPORT trial [3] and there is currently a randomised trial comparing protons with photons for prostate cancer (NCT01617161) [22]. Both studies come years after these technologies became accepted. The challenge remains to ensure that the evidence base for advanced technology is robust. There is a need for innovative, novel methodologies. One proposal is to use the IDEAL framework [23], comprising innovation, development, exploration, assessment and long-term studies (Table 1). By adding a stage for radiotherapy predicate studies covering all pre-clinical work, the R-IDEAL framework has been suggested [11,24].

Clinical Benefits

Introducing MR-IGRT is challenging. Fast adaptive daily planning for sites with significant tumour motion could improve the accuracy of treatment so that both local control and toxicity can be improved. Sites where MRI is already established as an important diagnostic tool may particularly benefit [25]. The potential advantages of MRI in prostate radiotherapy have been described [26]. MRI is already used routinely in brain and cervical brachytherapy planning, but the possibilities for integrating MRI further are exciting [27]. If IGRT can be delivered more accurately with real-time tracking and adaptive solutions then the imagined potential for dose escalation or the reduction of margins to

Table 1
R-IDEAL framework for the development of magnetic resonance (MR)-guided radiotherapy

		Purpose	Outcomes	Study design	Examples
Radiotherapy (predicate studies)	Stage 0	Technical – questions to be addressed before the use of MR-guided radiotherapy in man: – How do we use MR-guided radiotherapy? – Why use MR-guided radiotherapy and in whom?	Development of: – MR sequencing protocols, use of dedicated coils. – Inter-rater reproducibility testing. – Treatment strategies and patient selection.	Types of study: – phantom studies – inter-rater studies – planning studies – model-based studies	Inter- and intra-observer reproducibility of MR versus computed tomography delineation of the gross tumour volume in oesophageal cancer.
Idea	Stage 1	Technical – use of MR-guided radiotherapy, e.g. MR-linac for the first time to deliver standard treatment in a particular disease site.	Proof of concept	Type of study: – structure case report	(1a) MR-guided delivery of palliative radiotherapy for metastatic oesophageal cancer. 1b) MR-guided delivery of neoadjuvant CTRT with reduced planning target volume margins for stage IIB–IIIB oesophageal cancer.
Development	Stage 2a	Technical – develop and enhance MR-guided radiotherapy technology further.	Technical advancement, feasibility and safety testing.	Type of study: – small case series	Prospective cohort study of 10–20 patients with stage IB–IIIC oesophageal cancer undergoing neoadjuvant CTRT delivered with MR-guided radiotherapy (standard radiotherapy fractionation with reduced planning target volume margins). The aim is to optimise the technology and provide additional safety and efficacy data.
Exploration	Stage 2b	Clinical – proof of concept/efficacy and safety testing.	Early efficacy testing, focussing on: – dose distribution – target coverage – tumour response – local recurrence – toxicity – survival	Types of study: – prospective, randomised study – RCT or cmRCT – random allocation of MR-guided radiotherapy slots to eligible patients – non-randomised study with controls	Randomised study of patients with stage IB–IIIC oesophageal cancer treated with neoadjuvant CTRT using standard fractionation with reduced planning target volume margins on, for example, the MR-linac versus treatment with conventional margins delivered on a linac. Outcomes include pCR, toxicity, recurrence and 2 year survival.
Assessment	Stage 3	Clinical – compare MR-guided radiotherapy with standard treatment in a formal setting.	Comparison of efficacy versus standard treatment, focussing on: – disease-free survival – recurrence – toxicity – PROMS, CTC-PRO – economics/cost-effectiveness	Types of study: – RCT – cmRCT – registry-based trial	Multicentre RCT comparing: – mid- and long-term survival – toxicity – quality of life of MR-guided standard fractionation radiotherapy with reduced planning target volume margins versus standard radiotherapy in patients with stage IB–IIIC oesophageal cancer.

Long-term evaluation	Stage 4	Clinical – evaluation of the long-term outcomes of MR-guided radiotherapy and post-marketing investigations.	Review of long-term: – toxicity – disease-free survival – rare side-effects – CTC-PRO	Type of study: – prospective registries (all patients treated, for example, on the MR-linac)	Registration into a collaborative registry, e.g. by all MR-linac Consortium members of: – technical data – tumour characteristics – imaging – treatment – local control – survival – toxicity

R-IDEAL, radiotherapy-idea, development, exploration, assessment, long term evaluation; MR, magentic resonance; RT, radiotherapy; CT, computed tomography; GTV, gross tumour volume; CTRT, chemo-radiotherapy; PTV, planning target volume; RCT, randomised controlled trial; cmRCT, cohort multiple randomised controlled trial; pCR, pathological complete response; PROMS, patient reported outcome measures; CTC-PRO, common terminology criteria-patient reported outcomes.

minimise toxicity will become a reality. In the future, it may be possible to see, plan and treat all in the same day.

Summary

One of the next paradigm shifts in advanced radiotherapy will be that of MR-guided radiotherapy. Although there is much enthusiasm, there are a number of challenges that will need to be overcome. To facilitate the development of the MR-linac, an international consortium has been established to ensure that robust evidence is in place for clinical implementation. The collaborative efforts from seven large academic centres across two continents ensure that the best possible skills and talents are being used to make this exciting project a reality.

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