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MR-guided Radiotherapy: the Beginning of a New Era?

Over the last several decades, substantial technical innovations have paved the way for the delivery of highly precise and focused radiotherapy. These achievements can be primarily attributed to two sources: firstly, modern imaging technologies like computed tomography (CT), magnetic resonance (MR) imaging and positron emission tomography (PET) are increasingly incorporated in diagnostic evaluation and treatment planning, allowing for enhanced tumor delineation and secondly, the integration of imaging modalities directly into a linear accelerator have enabled daily monitoring of patient and tumor positioning as well as alterations in patient anatomy [1, 2].

Presently, CT-based image guidance has become standard-of-care, as CT imaging is routinely incorporated in nearly all radiotherapy units. However, low-dose CT imaging affords poor soft-tissue delineation and primarily allows for image guidance based on bony anatomy [3]. Conversely, MR offers excellent soft-tissue contrast allowing for precise target volume identification as well as monitoring of inter- and intrafractional changes in tumor positioning [4]. Given the technical challenges in integrating MR imaging into a linear accelerator, the first studies on MR-guided radiotherapy focused on offline solutions, with two different approaches proposed: either the patient was transported between the MRI and the linear accelerator or the MRI scanner was attached to rails on the ceiling to be moved out of the treatment room to ensure undisturbed operation of the linear accelerator [5–7]. At Heidelberg University Hospital and the German Cancer Research Center, we have prospectively treated patients with pelvic malignancies with offline, shuttle-based MR-guided radiotherapy and recently reported the efficacy, feasibility and patient compliance with this technique [8].

Nevertheless, all offline approaches are time-consuming effectively increasing the risk of intrafractional organ motion. Furthermore, the required patient re-positioning and associated positional inaccuracies challenge optimal radiotherapy delivery [6–8]. Naturally the radiation oncology community was eagerly awaiting the launch of the first hybrid machine incorporating a MRI scanner into the treatment delivery system [9]. Cobalt-60 teletherapy units were initially used for on-board MR imaging, but with recent advances and upgrades, linear accelerators are now increasingly utilized, with two hybrid devices currently available: the Viewray MRIdian Linac system (ViewRay, Oakwood Village, OH, USA), composed of a split-bore 0.35T MRI scanner, radiation gantry, and a 6 MV linear accelerator in the gap between the two magnet halves, and the Elekta MR-linac (Elekta AB, Stockholm, Sweden), composed of a 1.5T MRI scanner and a ring-based gantry containing a 7 MV standing wave linear accelerator [10–15].

The new MR-guided hybrid systems not only offer superior 3D imaging for precise tumor delineation as well as interfractional changes, but also provide 4D information via continuous monitoring of target volumes and surrounding critical structures for the treatment duration (cine MRI) [9, 13]. Compared to conventional radiotherapy techniques, safety margins and hence irradiated volume, can be decreased effectively reducing the risk of ensuing toxicity [12]. Encouraging initial results have been published for several tumor entities including pancreatic

carcinoma, early-stage low-risk breast cancer, and hepatic and adrenal metastases [16–19]. With some devices further offering gated dose delivery, neither the application of an internal target volume (ITV) nor invasive implantation of fiducial markers are needed for accurate motion management when using MR-guidance [9]. Respiratory gating and tumor tracking enable "real-time" anatomical feedback with the advantage of further reducing safety margins [20].

Beyond the aforementioned advances, the true potential of the new MR-guided hybrid devices lies in immediate, online adaptive treatment based on daily anatomical variation [18, 21]. MR-guided adaptive radiotherapy allows for the delivery of highly conformal treatments moulded to the current tumor position, enabling dose escalation to the primary target, with the potential for improved local control. Yet even without dose escalation, enhanced sparing of adjacent critical structures from dose spillage remains promising. Indeed, the initial studies identified primarily dosimetric advantages with online adaptation of MR-guided stereotactic radiotherapy of pancreatic, adrenal or ultracentral thoracic malignancies with additional clinical trial results highly awaited [16, 18, 22]. Radiation oncologists are now forced to reconsider the paradigms of total dose determination prior to treatment initiation and equal dose delivery for each fraction.

Beyond superior soft-tissue contrast, MRI also allows for incorporation of functional imaging, including non-invasive assessment of tissue perfusion, diffusion or cellular density [23, 24]. The potential availability of on-board 'functional' MRI sequences may allow for biologic, in addition to geometric, adaptation. For example, diffusion-weighted imaging (DWI) not only facilitates the identification of diffusion-altered tumor from surrounding healthy tissue, but also enables quantitative evaluation of suspicious lesions by using the apparent-diffusion coefficient (ADC), which correlates with cellularity and has been shown to be predictive for treatment responseto radiotherapy, as previously examined with rectal tumors [25, 26]. Hence, functional imaging might support early identification of nonresponders who may benefit from dose escalation. Future studies will answer whether daily on-board functional imaging is necessary or whether weekly offline imaging is sufficient for predicting treatment response. Currently, only 0.35T and 1.5T on-board MRI imaging is offered, misjudging the true potential of MR guidance. High-end diagnostic MRI scanner offer superior imaging quality for assessing tumor response and even potential treatment-related toxicity. A recent study illustrated the high benefit of 3T-MRI for predicting pathological treatment response following neoadjuvant radiochemotherapy for pancreatic cancer [27]. High-field or even ultra-high-field MRI further enables not only functional but also molecular imaging for even more precisely identifying tumor volumes, characterizing radioresistant tumor regions before radiation therapy and detecting recurrent disease following treatment [28]. Chemical exchange saturation transfer (CEST) MRI was recently reported to serve as a predictor of early progression in glioblastoma patients [29, 30].

A further highly promising scenario is MR-only planning bearing the potential of reducing not only radiation exposure as well as uncertainties introduced by CT-MRI registration but also additional work and costs. The major challenge for such an MR-only workflow is the development of so called pseudo-CT images for accurate dose calculation and planning. However, a number of techniques have been proposed for generating synthetic CTs from MRI data. Initial promising results for treatment planning of brain, prostate, head-and-neck, and pelvic tumors have already been published [31]. These studies illustrated that MR-only based radiotherapy might not only promise superior target delineation but also the potential for equivalent treatment planning. In future, the leading role of CT in radiotherapy might be replaced by MRI with its numerous advantages.

Despite the potential benefits of MR-guided radiotherapy, significant improvements are needed before widespread adoption and implementation. Available autosegmentation programs require significant manual adjustments, extending treatment times and increasing the risk of intrafractional motion; this is actually one reason why currently MR-guided radiotherapy primarily focus on hypofractionated stereotactic treatment of small lesions: due to the sharp dose gradient in stereotactic radiotherapy, re-contouring and re-optimization of daily plans can be quickly performed by only adapting those structures in close proximity to the target volume – a technique which can only partly be transferred to conventionally fractionated radiation of larger target volumes [11]. Furthermore, software tools for deformable dose accumulation are lacking, such as dose summation of different adapted fractions with varying organ and tumor volumes. Hence, the cumulative dose with dose maximum, minimum, and mean for every organ at risk cannot be provided, deterring any possibility of re-irradiation in the future.

Given that MR-guided adaptive radiotherapy requires significant time as well as an experienced team of professionals, clinical trials are needed to identify which patients will benefit most from adaptive treatment. However, direct comparisons between CT- and MR-guided adaptive radiotherapy using conventional fractionation may not accurately capture the true potential of MR-guided adaptive radiotherapy, given that MR-guided adaptive radiotherapy allows for high dose delivery under circumstances which would not otherwise be possible with conventional techniques [27].

Although there are many remaining challenges, MR-guided adaptive radiotherapy offers an unique chance for customized, daily individualized radiotherapy for further reducing side-effects in cancer therapy and improving tumor control and survival.

I hope you enjoy reading about the many new advances in MR in RT that we present to you in this magazine.

Jürgen Debus

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