Editorial Commentary

Magnetic resonance imaging-guided stereotactic body radiotherapy for prostate cancer: more than a simple "MIRAGE"?

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Ultra-hypofractionated stereotactic body radiation therapy (SBRT) for localized prostate cancer (PCa) is emerging as a safe and effective treatment alternative to normo-fractionated and moderate hypo-fractionated radiation regimens (1-4). It has been recently proposed as a new therapeutic standard by National Comprehensive Cancer Network (NCCN) guidelines (2) for low-risk, intermediate-risk, and in selected cases of high-risk PCa.

Routine implementation of magnetic resonance imaging (MRI) linacs represents a breakthrough innovation in the radiation oncology field, with a potential gain in terms of accuracy in treatment delivery thanks to a better visualization of target volumes and real-time plan adaptation (5). However, to date, the translation of such technology into an improved clinical outcome compared to state-of-the-art linac-based technology is less clearly established.

With the results of their open label, single institution, phase III, MIRAGE trial, Kishan *et al.* were able to shed light on the added value of this technology for the treatment of PCa (6). Comparing the incidence of grade ≥2 genitourinary (GU) and gastrointestinal (GI) toxicity of PCa patients randomized to an MRI-guided SBRT (with 2-mm planning margins) *vs.* a computed tomography (CT)-guided SBRT (with planning margins of 4 mm), the authors demonstrated a significantly lower incidence of acute Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grade ≥2 GU toxicity rates when SBRT was guided by MRI compared to CT imaging (24.4% *vs.* 43.4%, P=0.01). Similarly, patients treated with an MRI-guided SBRT showed a better toxicity profile even in the GI domains and several patient-reported outcomes at 1-month of follow-up.

While the authors should be congratulated for conducting this important trial and the results are undoubtedly of great interest, this study offers several points for discussion.

In the context of prostate SBRT treatments, the optimal radiotherapy dose and fractionation schedule remains yet to be determined. In the MIRAGE trial, the delivered dose was 40 Gy in 5 fractions on alternate days prescribed to

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the planning target volume (PTV) (6). Not surprisingly, the acute urinary toxicity rate of the CT-guided SBRT arm of the MIRAGE trial was higher than the acute toxicity observed in the PACE-B international, phase 3, randomized, non-inferiority trial testing SBRT *vs.* moderate hypo-fractionated RT for localized PCa. In the PACE-B trial a 40 Gy dose was delivered to the prostate but with a dose-reduction to the PTV (36.25 Gy), an optimization to the urethra, and implementation of intrafraction motion control using a robotic arm delivery system in almost half of the SBRT patients (approximately 21% of acute CTCAE grade ≥2 GU toxicity) (7).

On the other hand, the rate of acute grade ≥2 GU toxicity was comparable to patients treated in the CT-guided SBRT phase II randomized PATRIOT trial evaluating the impact of overall treatment time delivering a homogenous dose of 40 Gy with an isotropic 5-mm margin [32.9% and 36.5%, the Radiation Therapy Oncology Group (RTOG) grading scale, for patients treated every-other-day or once weekly, respectively] (8).

As the benefit of dose escalation remains to be defined in the setting of prostate SBRT, use of protracted SBRT regimens using once weekly schedules (9-11), implementation of focal dose escalation to the dominant intraprostatic lesion (12), or delivery of urethra-sparing techniques (13), are emerging strategies to mitigate the differences in terms of toxicities observed in the MIRAGE trial between the CT- and the MRI-guided arms.

The volumetric impact of moving from a 4-mm isotropic margin with a CT-guided SBRT to a 2-mm margin using an MRI-guided SBRT is doubtless. If an isotropic 2-mm PTV margin is not a clear standard for SBRT treatments, with the use of online correction protocols and tracking assistance, it seems realistic to push the limit at this level also for CT-guided SBRT treatments (14). Notably intrafraction motion control systems like use of electromagnetic transponders (15) or single/stereoscopic X-ray imaging of implanted markers (16) are commercially available and installed on standard linacs.

Some authors have recently proposed and clinically applied a sub-fractionation workflow for magnetic resonance (MR)-guided SBRT to allow for a reduction of intra-fraction uncertainties, thus reduced PTV margins, at the cost of a 42-minute treatment time on average per fraction (17). In comparison, the fast beam-on time of CT-guided SBRT using volumetric delivery techniques [volumetric-modulated arc therapy (VMAT)] does clearly better than the MRI-guided SBRT treatments using multiple-field intensity-modulated radiation therapy (IMRT) techniques (in the MIRAGE trial, the median post-imaging delivery time was 232 seconds in the CT-arm compared to 1,133 seconds in the MR-arm). Not only a better reproducibility related to the shorter treatment times, but a better inter-operator variability in treatment planning can also be expected using a VMAT technique compared to a multiple-field IMRT (18).

Nevertheless, it is undoubtful that MRI-guided SBRT with daily online adaptive is an emerging technique with a great potential for mitigation of radiation-induced toxicities. As shown by a recent systematic review and meta-analysis, MR-guided adaptive SBRT is associated with a significantly reduced risk of acute grade 2 or higher GU or GI toxicity compared to a fiducial or CT-guided non-adaptive prostate SBRT (12% and 5% on average, respectively) (19).

In summary, the results of the MIRAGE trial are a clear step forward in the optimization of SBRT treatments for PCa. While implementation of new technologies in the routine clinical practice has the potential to translate in a clinically measurable benefit, the best way to deliver SBRT treatments to PCa patients probably remains yet to be defined.

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