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20 Years of MRI-guided Brachytherapy for Adaptive Radiation Oncology

Dear readers and colleagues,

This 7th edition of the *MReadings: MR in RT* contains a wide range of very interesting articles describing the integration of MRI into radiation oncology. Many of these individual experiences are similar to the long process of introducing MRI into brachytherapy. MRI-guided radiotherapy for external beam adaptive radiation oncology became an essential modality during recent years [1, 2]. Its use for brachytherapy already has a history that spans more than two decades. Initial experiences have been reported for several clinical disease sites, but clinical application in the treatment of gynecological and prostate cancer has been described by far the most [3]. For cervical cancer therapy, MRI-guided brachytherapy became state of the art in daily clinical routine. Back in 1992, Schoeppel et al. [4] described the use of "magnetic resonance imaging during intracavitary gynecologic brachytherapy" and showed the relation between the dose delivery device, the brachytherapy applicator, and the surrounding anatomy, especially the tumor. Mayr et al. identified in that early period the clear benefit of MRI in addition to clinical examination and with a clear advantage compared with CT-based tumor delineation [5].

MRI for brachytherapy is well established at the Department of Radiotherapy (now Radiation Oncology), Medical University of Vienna (known at that time as the University of Vienna) in Austria. There, a dedicated MR scanner for radiotherapy was installed as early as 1997 under Professor Richard Pötter. With the idea of using it together with the Division of Interventional Radiology, a low-field, open bore scanner was chosen (MAGNETOM Open Viva 0.2T, Siemens Healthcare, Erlangen, Germany). There was no specific support from the industry for its use in radiotherapy or brachytherapy. This created a substantial demand for research and development as well as quality assurance, especially taking into account image acquisition and distortion [6]. Essentially, it was possible to achieve high accuracy in the center of the field and in the pelvic area [7]. In brachytherapy, this region contains the delivery device, the applicator, and the clinical target volume. It was therefore possible to introduce MRI for cervical cancer brachytherapy clinically in 1999 [8]. Another advantage of MRI for brachytherapy application is the energy spectrum: The use of Iridium-192 instead of the higher energies used with Cobalt-60 or linear accelerators means that the energy spectrum and the predominant Compton effect allows dose planning based on water equivalent assumptions without clinically relevant uncertainties inside the pelvis [9].

Still, the misconception remains that brachytherapy treatment planning needs additional CT imaging to enable accurate dose calculations. Furthermore, there is a myth that only deformable image registration would allow the combination of external beam radiotherapy and brachytherapy for cervical cancer. However, the homogenous

external beam dose present at those volumes and organ parts that are of main interest for total dose constraints (external beam plus brachytherapy) allows a very good dose estimation without deformable image registration. There are even major limitations from the underlying target concepts so that it is questionable that such methods would result in a clinical benefit or improvement of the workflow [10].

The main issue in the initial phase of MRI integration in brachytherapy treatment planning was the lack of treatment planning software with the option to import sectional imaging from MRI. First, sectional images in general were not supported, later it was still difficult to import non-axial, oblique image orientations. The interim solutions for the first clinical applications were then based on the already state-of-the-art 3D reconstructions with orthogonal or semi-orthogonal radiographs (often called 2D planning, although the two radiographs allowed the reconstruction of the applicator and anatomical points in 3D). Applicators and some limited anatomical structures were digitized. These 3D datasets were used for dose calculation and could subsequently be registered to axial MR images for dose evaluation. The first rigid registration of radiographic approximation and MRI was established. The evaluation of isodose lines directly visualized on MRI slices was a major development and a particular advantage in daily clinical practice. Suddenly, the dose to individual parts of the tumor, the clinical target volume, and to organs and their substructures could be analyzed in detail. However, in first instance this did not result in reproducible plan evaluations and dose prescriptions at all. The first major step was the calculation of dose volume histograms for structures directly contoured on MR slices [11]. Although this was performed in daily clinical practice, the workflow itself became extremely time-consuming until the first planning systems to allow direct reconstruction of the brachytherapy source path and contouring in one MRI dataset, also consisting of several image orientations. This resulted in the first clinically applied MRI-only treatment plans in radiation oncology.

Image orientation was an essential topic, as the radiation oncologist performing the brachytherapy was used to an applicator's eye view – comparable to the beam's eye view in external beam. MRI with its possibility to orientate the slice orientation perpendicular to the tandem applicator located in the intrauterine channel was a major step toward the development of contouring guidelines with reduced inter- and intraobserver variations [12].

The clinical target definition and appropriate concepts for dose prescribing, recording, and reporting became essential when introducing MRI. The initial experience in Vienna demonstrates this process [13]. The clinical outcome in terms of local control improved substantially. Especially for larger tumors, the local control increased from 64% in 1998–2000 to 82% in 2001–2003. And even more importantly, this increase in tumors larger > 5 cm was related to significant improvement in overall survival from 28% to 58%.

What were the main reasons for this success?

Target concept and dose metrics for prescribing and reporting

From my personal experience, the initial phase started with a major breakthrough: MR images at diagnosis with their soft-tissue contrast showing the gross tumor volume (GTV) with high signal intensity as well as the entire cervix, uterus, and, especially, potential infiltration into the parametrium were not new. A special learning phase included the understanding of MRI at the time of brachytherapy, in particular, the residual GTV and definition of gray zones, areas of tumor infiltration at diagnosis with a response to the external beam treatment usually performed prior to brachytherapy. But showing isodose lines in relation to these volumes of initial GTV, residual GTV, and a high-risk CTV (including gray zones) and analysis of dose volume histograms were the major step forward. However, without a clear target concept, inter- and intraobserver variations for the contours were huge and treatment plans were highly individual. Dose variations for target and organs at risk were substantial and lacked clear dose constraints.

These imaging and technological advances provided the initial impulse for groups like ICRU and GEC-ESTRO to found working groups. Richard Pötter from Vienna, together with Christine Haie-Meder, Villejuif, Paris, France, and Erik van Limbergen, Leuven, Belgium, representing different traditional treatment schools for cervix cancer radiotherapy succeeded in agreeing on a detailed target-concept and dose-reporting concept. From the beginning, these groups included medical physicists. Their concept was based on MRI with integration of the information from the clinical examination. It provided the basis for the internationally successful GEC-ESTRO recommendations I and II, two of the most cited articles in radiotherapy and oncology [14, 15]. The GEC-ESTRO recommendation III was dedicated to the principles and parameters of MR imaging within the framework of image-based adaptive cervix cancer brachytherapy [16] while part IV added the essential component of 3D registration [17]. All of these guidelines were finally extended to the international ICRU 89 report, supported by experts from Europe, North America, and Asia [18]. This comprehensive report allowed to define target volumes and organs at risk and provided a clear concept for prescribing, recording, and reporting dose. Definition of the initial GTV, residual GTV, as well as a risk-based clinical target volume concept using MRI are a key message in this report.

Optimizing dose delivery

The second major issue was dose delivery. The sudden clear picture of target volumes and organs at risk in relation to the dose distribution revealed major limitations of the application techniques that had been applied so far in daily clinical practice as "state of the art" based on standard point A dose prescription. Dose optimization by changing the dwell-time distribution could only partially compensate for the limited dose coverage. Especially large tumors and situations with unsuitable topography of target and organs at risk could not be sufficiently covered.

Optimized dose delivery became possible mainly by increasing the degrees of freedom with additional applicators placed inside the target volumes. Pioneering work has been done by developing compatible applicators and their visualization on MRI. This has been described first by using interstitial needles for the prostate especially, but also titanium needles [19, 20]. Especially the use of non-metallic tandem-rings and tandem-ovoid applicators in combination with these types of needles, visualized directly on MRI, allowed highly individualized dose distribution [21]. Dose could be increased to the clinical target volumes and gross tumor volume without increasing dose to surrounding organs. For asymmetric tumor topography, it allowed a higher conformality and often even a decrease in organ dose.

Adaptive workflow

Another major development was the adaptive workflow compared with image-guided external beam therapy. From the very beginning of fractionated high-dose-rate brachytherapy, a fully adaptive process was performed. MRI at the time of diagnosis and MRI at the time of brachytherapy (usually after a major amount of external beam dose delivery) allowed to study the pattern of response for the specific tumor situation. This allowed a detailed target definition based on GTV at diagnosis, the residual GTV, and the visible situation at the time of treatment.

Offline MRI is used by performing a pre-treatment MRI. This method allows to get the tumor situation at diagnosis and after external beam the radiochemotherapy response at a timepoint directly before brachytherapy. In such cases, the pre-treatment MRI is used to delineate the GTV and CTV on conventional CT plans.

However, online, MRI-guided interfraction adaptive RT became the real state of the art. In one sequence, it visualizes the GTV, CTV, organs at risk, the dose delivery device, and brachytherapy applicators with a high degree of accuracy. It would be comparable to an image visualizing the tumor, the organs, and the linear accelerator all at once. Only small uncertainties are introduced during the final dose delivery even hours after contouring and treatment planning. This was demonstrated in multiple studies, even resulting in a special issue of the Green Journal (multicenter analysis of uncertainties in [22]). These "intrafraction" variations are limited as demonstrated by repeated MRI scans after or directly before dose delivery for a second time.

Key to all the aforementioned developments was the highly interdisciplinary approach. All major guidelines and studies were generated through an intensive and balanced interaction between radiation oncologists and medical physicists as major contributors.

The integration of MRI into the brachytherapy planning process resulted in considerable improvements in treatment planning with an increase in target coverage and dose as well as a decrease in OAR doses. This was expected to translate into clear clinical benefits. This process could only become successful with clinical concepts including adaptive radiotherapy, adaptive in terms of adaptation of the target volume at the time of boost treatment (brachytherapy), adaptation of application technique, and optimized dose delivery.

And 20 years later? What is the status now? After several encouraging retrospective mono-institutional reports, it took a long time until a clear benefit of all these efforts could finally be demonstrated through a prospective clinical trial. The observational, multi-center EMBRACE I trial has provided comprehensive evidence that MRI works for radiotherapy (brachytherapy) of cervical cancer in clinical practice (1,416 patients from 24 centers from 2008–2015) and leads to excellent clinical results. The evidence relates to technology (MR imaging and the introduction of interstitial brachytherapy), dosimetric parameters (high target doses, also in advanced disease and limited OAR doses), as well as disease and morbidity outcomes. Local control was 92% at 5 years and was not significantly different between more limited and advanced local tumor stages (IB2-IVA). Overall survival at 5 years was outstanding at 74% [23].

MRI-based, image-guided, adaptive brachytherapy therefore represents a paradigm shift in the treatment of cervical cancer. It is currently leading to a change in clinical practice in Europe, North America, and in Asia. For any future developments, this MRI-based treatment approach should be used as the benchmark.

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