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Professional Paper

MRI-GUIDED RADIOTHERAPY FOR PROSTATE CANCER: A NEW PARADIGM

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ABSTRACT: Radiotherapy is one of the key treatment modalities for primary prostate cancer. During the last decade, significant advances were made in radiotherapy technology leading to increasing both physical and biological precision. Being a loco-regional treatment approach, radiotherapy requires accurate target dose deposition while sparing surrounding healthy tissue. Conventional radiotherapy is based on computerized tomography (CT) images both for radiotherapy planning and image-guidance, however, shortcomings of CT as soft tissue imaging tool are well known. Nowadays, our ability to further escalate radiotherapy dose using hypofractionation is limited by uncertainties in CT-based image guidance and verification. Magnetic resonance imaging (MRI) is a well established imaging method for pelvic organs. In prostate cancer specifically, MRI accurately depicts prostate zonal anatomy, rectum, bladder, and pelvic floor structures with previously unseen precision owing to its sharp soft tissue contrast. The advantages of including MRI in the clinical workflow of prostate cancer radiotherapy are multifold. MRI allows for true adaptive radiotherapy to unfold based on daily MRI images taken before, during and after each radiotherapy fraction. It enables accurate dose escalation to the prostate and intraprostatic tumor lesions. Technically, MRI high-strength magnetic field and linear accelerator high energy electromagnetic beams are hardly compatible, and important efforts were made to overcome these technical challenges and integrate MRI and linear accelerator into one single treatment device, called MRI-linac. Different systems are produced by two leading vendors in the field and currently, there are around 100 MRI-linacs worldwide in clinical operations. In this narrative review paper, we discuss historical perspective of image guidance in radiotherapy, basic elements of MRI, current clinical developments in MRI-guided prostate cancer radiotherapy, and challenges associated with the use of MRI-linac in clinical practice.

Key words: *prostate cancer, MR-linac, image-guided radiotherapy, online adaptive radiotherapy, MR-guided radiotherapy*

Role of imaging in radiotherapy

Over 6 decades, the radiation delivered with linear accelerators has been the mainstay radiotherapy treatment option for localized prostate cancer. The rapid technological progress has been characterized by

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several major steps and leaps forward (1). Evidently, the most recent era of MRI-guided radiotherapy represents profound change in the paradigm of perceiving and treating prostate cancer (2).

Imaging has always been crucial in the radiotherapy planning and delivery. In the sixties, the standard collimator was first shaped and deployed in delivering radiotherapy with the capacity to reduce RT complications compared to cobalt-60 delivery. In the seventies, cerrobend blocks were used in order to reduce the dose received by normal tissue using 2-D radiotherapy rectangular fields. The next technical milestone was reached in the eighties with the development of multi-leaf collimator (MLC) leading to clinical use of 3D-conformal radiotherapy which allowed for the first dose escalation trials. In the nineties, a further step was reached with the advent of dynamic MLC and new RT technique called intensity modulated radiotherapy (IMRT) with inverse planning, which allowed for further dose escalation and reduction in normal tissue complication probability. After the 2000s, high resolution IMRT was developed, allowing for smaller subfields and daily image guidance. Nowadays, dynamic IMRT techniques, such as volumetric modulated arc therapy (VMAT) became highly employed and helped in achieving excellent target coverage with simultaneous normal tissue sparing. In parallel, new imaging modalities were introduced such as multi-slice CT, wide cone beam CT (CBCT), MRI, hybrid units that combine positron emission tomography, and computerized tomography (PET/CT). These allowed for a more precise and accurate imaging that was progressively adopted in radiotherapy (3). Broadly, there are three main areas of application of modern imaging in RT (4)while avoiding normal tissue injury. Imaging for cancer diagnosis, staging, treatment planning, and radiation targeting has been integrated in various ways to improve the chance of this occurring. A large spectrum of imaging strategies and technologies has evolved in parallel to advances in radiation delivery. The types of imaging can be categorized into offline imaging (outside the treatment room:

a) Treatment planning
b) Treatment response assessment
c) Treatment localization and delivery

During treatment planning, high quality imaging is crucial to accurately delineate the target (typically gross tumor volume, GTV or tumor bed). On the next level, functional imaging, if available, helps clinicians to define high-risk volumes. Using imaging, we may also assess treatment response during or after treatment. This would allow a clinician to trigger some adaptive approaches and personalize radiotherapy tailored to patient response. The key prerequisite of radiotherapy is accurate treatment localization and delivery, with the need to address target motion. Here, on-board imaging with or without fiducial markers, have a potential to mitigate possible geographical miss as a result of target motion between the fractions and also within a single fraction (5).

Image-guided radiotherapy (IGRT) has been rapidly adopted in clinical practice. In the seminal paper by Simpson et al., the proportion of IGRT methods increased to 90% of all RT protocols by the year 2010 (6). Precisely, the three modalities experiencing the steepest growth in RT imaging applications were 4-D CT, 18-FDG-PET/CT and MRI and were mainly applied in head and neck and genitourinary cancers, and CNS tumors.

Role of MRI in radiation planning and treatment

For treatment planning in prostate cancer, CT and MRI are inter-compatible modalities. CT has high spatial resolution, while MRI offers excellent soft tissue contrast providing detailed anatomical definition of structures of prostate, intraprostatic zones, prostate capsule, bladder, rectum, anorectal wall, etc. (7). Although pretreatment CT imaging is still a cornerstone for the accurate dose calculation based on tissue attenuation properties represented by Hounsfield units, the use of only MR imaging for treatment planning has also been a subject of recent investigations, especially for prostate cancer patients (8). This could potentially make the clinical workflow with integrated machines even simpler and faster.

When considering the role of imaging in treatment response assessment, it is important to emphasize that MRI enables personalized or adaptive radiotherapy through functional imaging such as diffusion-weighted imaging (DWI), dynamic contrast-enhanced imaging (DCE), magnetic resonance spectroscopy (MRS).

In treatment delivery, MRI allows accurate target tracking and radiation beam gating during the treatment, which results in improved precision of dose delivery and better local control rates (9)feasibility and patient tolerance were prospectively assessed using patient-reported outcome questionnaires (PRO-Q.

When taken together, these systems combine MRI imaging and RT delivery capabilities to scan the patient during and after the treatment, to evaluate response and to adapt treatment depending on the response observed on imaging providing an opportunity to improve the quality of our delivery. Such devices are called integrated MRgRT systems (10).

There are several key assumptions when considering MRgRT adoption in clinical radiotherapy:

a) Soft tissue contrast could be further improved in radiotherapy
b) Aiming at no extra radiation dose from IGRT procedures
c) Motion management may improve clinical outcomes
d) Inter-fractional variations may impact RT quality

There are four key domains into which we could group potential benefits that MRI provides for IGRT. In the area of soft tissue visualization, MRI makes difficult-to-image targets and critical structures easily distinguishable, allows improved ability to adapt treatment and ability to see the tumor, and not just the organ surrogate for GTV (traditionally, the whole prostate is considered as GTV in spite of the fact that there is a tumor only in a portion of the gland, mostly in the peripheral zone). In the sphere of real-time 2D and 3D imaging, MR imaging is taken simultaneously with irradiation, and gating or tracking is made possible without surrogates. The fact that MRI produce no ionizing radiation allows more frequent imaging assessment to monitor anatomical response. Finally, frequent tumor response assessment, both inter- and intra-fraction, allows cumulation of quantitative imaging data which can be used for radiomics analysis and response assessment and can potentially lead to the identification of prognostic and predictive factors (5). Related to inter-fractional motion, daily patient anatomy situation can be assessed and therefore better dose conformality with tighter PTV margin and better OAR sparing can be achieved. Considering the intra-fractional motions, adaptive gated beam delivery can be achieved by continuous tracking of target and organ motions.

Elements of MR-guided-radiotherapy workflow

There are several elements to be considered when deciding what is the optimal target for MRgRT (11) providing volumetric imaging at excellent soft tissue contrast, is expected to provide novel possibilities in the implementation of image-guided adaptive radiotherapy (IGART. The 'perfect' target should be located within anatomical sites with similar electronic density i.e. Hounsfield units (on CT), like in abdomen and pelvis where it is hard to distinguish anatomical boundaries of visceral organs and soft tissue structures. To experience the benefits of accurate organ/target tracking and gating, a target needs to be mobile, both within the single fraction and between each fractions. Next, target should be in the proximity to sensitive organs-at-risk (the example of duodenum, rectum). Finally, the accumulation of MRI imaging data should provide valuable information (like shrinkage or early toxicity onset thus enabling radiomics application).

Probably owing to previously discussed factors, pelvic sites accounted for 11% of all MRgRT usage in a large single-center analysis (12).

Due to the adaptive nature of MRgRT workflow, there is a need for systematic approach to decide when to adapt the treatment. Here, several factors need to be considered.

First, patient characteristics, such as patient compliance and modification during the treatment, should be considered. Second, one needs to establish anatomical changes thresholds (i.e. organ displacement or filling). Third, how to deal with dosimetric changes, when there is a difference between predicted and re-optimized dose, when to change fractionation, etc. In general, compared to CT based radiotherapy, MR based radiotherapy is more dynamic and requires the integration of decision making in all steps of radiotherapy workflow (13).

Currently, there are two clinically deployed integrated/hybrid MRgRT solutions: ViewRay MRIdian ((ViewRay Inc., Oakwood, USA) and Elekta Unity (Elekta, Stockholm, Sweden). ViewRay provided the first FDA cleared MRI-Guided Radiation Therapy device. The Elekta Unity MR-linac was approved for clinical use by the U.S. Food and Drug Administration (FDA) for patient treatments in 2018, making it the second commercially available MR-linac. These two commercially available MRgRT devices are significantly different both in terms of linac and MRI specifications

The ViewRay system combines 0.35 T MRI scanner with highly performing linac capable of rotational IMRT delivery, with split magnet design allowing beam penetration and reducing scatter radiation. In that way, the radiation beam produced by linac is not affected by magnetic field. In the low magnetic field, the strength effect of magnetic field on dose distribution is considered negligible, and spatial integrity is good, being of 2 mm order.

Elekta Unity relies on high magnetic field strength of 1.5 T resulting in high MR image quality, coupled with linac producing 7 MV flattening filter-free photon beam for radiation therapy. Linac gantry relies on slip-ring technology allowing continuous rotation around MRI system thus showing no visible collimator or light field and having a larger source to isocenter distance of 143.5 cm than conventional RT units. Available treatment technique is the step- and-shoot IMRT with 7.2 mm wide MLCs at isocenter.

The typical clinical workflow with hybrid MRgRT machine still involves pretreatment CT imaging on separate CT simulator which is registered with daily MRI taken on MRI-linac (14). The illustration of the paradigm change introduced by MRgRT in the radiotherapy workflow, enabling real time adaptive radiotherapy, is presented in the Fig. 1. In traditional IGRT workflow, if our target changes (i.e. CTV) based on interval imaging, replanning and adapting is needed. In order to do that, repeated patient imaging is required in order to be able to deliver a new plan. In the new workflow, real time adaptive MRgRT can be done using more dynamic adaptation process that is based on on-line re-optimization and re-adapting the treatment that can be done with daily patient imaging with high quality MRI. There are different approaches to daily treatment adaptation by recalculation or re-optimization of the initial plan to include either new patient position or difference in patient anatomy. Both ways rely on image registration between simulation CT scan and online MR image (15).

Challenges related to clinical application of MRgRT

There are also some technical challenges related to MRgRT workflow (5). As in other procedures that involve radiation application in medicine, a quality assurance (QA) and quality control (QC) of equipment and procedures need to be implemented and followed rigorously to assure overall precision and safety. Usual QC procedures in conventional and other advanced RT techniques need to be supplemented taking into consideration the unique design of MRgRT units with specific geometry and the presence of magnetic field during treatment that both affect radiation dose distribution. QA of mechanical, dosimetrical and image quality performance pose the challenge, in medical physics field, to provide a comprehensive QC programme that generally consists of three main parts similar to conventional IGRT linac with onboard CBCT. Firstly, it is the QA of the linac part specially adjusted for above mentioned special features of MRgRT unit, then image quality of the MRI part including magnetic field homogeneity, signal-to-noise ratio and known problem of geometrical distortion, and finally QA of the coordinate alignment between imaging and treatment isocenters. Special attention in the choice of adequate equipment for performing these tests is also needed; materials used should be MR safe, and the results should not be affected by the magnetic field presence. The overview of suitable equipment and QC procedures is given in a recent report of the MRI-linac consortium by Rob-

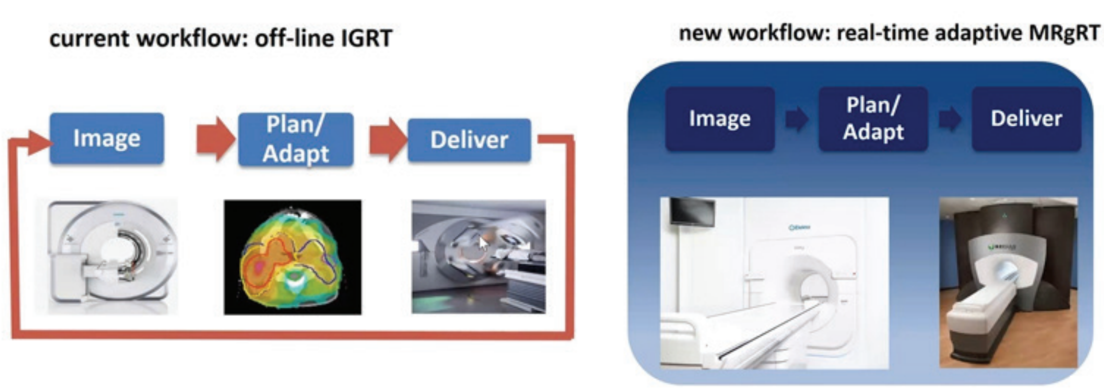

Fig. 1. Comparison of off-line IGRT with real time adaptive MRgRT

erts et.al. (16). Authors relate either to the machine QC, new phantoms needed for dose calculation, dosimetry, and beam verification. Furthermore, MRI is known to be associated with geometric distortions, lack of electron density information, need for optimized imaging sequences, lack of auto-segmentation and need for coils. Regarding the patient safety, staff should be mindful of MRI compatibility of patient implants, allergic reactions to contrast agent and patient claustrophobia. Finally, the most demanding would be the development and introduction of tools and procedures for adaptive radiotherapy that allow functional imaging integration, radiobiology based adaptive radiotherapy, dose painting, and accumulated dose mapping (17)so that the tumor is exposed to a high dose, whereas nearby healthy structures can be avoided. As a result, an increase in curative dose is no longer invariably associated with an increased level of toxicity. This modern technology can be exploited further by modulating the required dose in space so as to match the variation in radiation sensitivity in the tumor. This approach is called dose painting. For dose painting to be effective, functional imaging techniques are essential to identify regions in a tumor that require a higher dose. Several techniques are available in nuclear medicine and radiology. In recent years, there has been a considerable research effort concerning the integration of magnetic resonance imaging (MRI.

Conclusion

In conclusion, MRgRT is a promising tool to deliver high quality, precise, real time adaptive radiotherapy, which relies on the diagnostic MR image quality allowing for improved visualization of the target and organs-at-risk when high soft-tissue contrast is needed. Real-time workflow is very useful and allows for MRI-guided adaptation of the treatment but also for the monitoring of the motion between the fractions and within the same fraction. Functional imaging can further provide useful information to the clinician. Also, there is possibility to perform dose accumulation studies both within the target and the segments of organs-at-risk. On the next level, there is a high potential forMRgRT technology to facilitate the reduction in the number of treatment fractions, specifically relevant to prostate cancer where moderate hypofractionation has become standard of care but can still be optimized in terms of delivery. Furthermore, by reducing treatment margins, MRgRT allows for lower dose at organs-at-risk and higher target dose. By using MRI-based morphological and functional imaging, it is possible to introduce individualized dose concepts and perform response-adaptive treatment. Finally, MRgRT opens the way for new radiotherapy indications and new approaches to deliver innovative radiotherapy in the areas not normally explored in the routine clinical practice.

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Sažetak

RADIOTERAPIJA RAKA PROSTATE VOĐENA MAGNETSKOM REZONANCOM: NOVA PARADIGMA LIJEČENJA

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SAŽETAK: Radioterapija je temelj liječenja raka prostate. Radioterapija je zadnjih godina značajno napredovala što je omogućilo njenu preciznost. Radioterapija zahtjeva točnu isporuku radioterapijske doze na tumor uz maksimalnu poštedu okolnog zdravog tkiva. Konvencionalna radioterapija se bazira na slikama kompjuterizirane tomografije (CT) za sve faze radioterapijskog procesa, iako su slike CT-a slabe rezolucije za prikaz mekih tkiva. Danas je naša sposobnost da još više podižemo radioterapijsku dozu limitirana nedovoljnom jasnoćom CT slika. Magnetska rezonanca (MR) za razliku od CT-a ima odličan kontrast za meka tkiva zdjelice te odlično oslikava prostatu i zdjelične strukture. Mnoge su prednosti uključenja MR u radioterapijski proces raka prostate. MR omogućava pravu adaptivnu radioterapiju na osnovi MR slika uzetih prije, tijekom i nakon radioterapije. Omogućuje eksalaciju doze na intraprostatičke tumorske strukture. Napredak tehnike je omogućio integraciju snažnog magnetskog polja MR-a i visokoenergetskih X-zraka linearnog akceleratora u jedan jedinstveni uređaj - MRI-linac. Dva su MR-linac komercijalna sustava dostupna na tržištu, a u svijetu ima instalirano preko 100 ovakvih uređaja. U ovom preglednom članku razmatramo razvoj slikovnog vođenja u radioterapiji, trenutno stanje magnetom vođene radioterapije raka prostate, kao i izazove u primjeni ove inovativne metode.

Ključne riječi: *rak prostate, MR-linac, slikovno vođena radioterapija, online adaptacija radioterapije, radioterapija vođena magnetskom rezonancom*