

MR-only guided proton therapy: advances, future perspectives and challenges

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Introduction

At the end of January 2018, proton therapy was introduced at the University Medical Center Groningen (UMCG). The Groningen Proton Therapy Center (GPTC) is one of approximately 60 proton therapy centers in operation worldwide. Over the last decade, the number of proton therapy centers has been constantly increasing. Proton therapy allows for radiation of tumor tissue with high precision, while minimizing normal tissue damage. This is due to the intrinsic physical properties of protons that allow for decrease of radiation dose issued to tissue surrounding the target volumes compared to conventional photon therapy [1, 2]. However, to fully utilize the benefit of protons, very accurate identification of tumor location is required. The advantage of highly conformal dose distributions in proton therapy may be compromised by spatial distortions, as they increase the range uncertainty of the proton beam. Due to the energy deposition of protons with steep dose gradients, accurate positioning of these gradients is critical to successful treatment planning and treatment delivery [1]. Geometric errors and uncertainties in Computed Tomography (CT) and Magnetic Resonance (MR) images can have a significant dosimetric impact, especially when the radiation is targeted to a small volume or a volume close to organs at risk [3]. In other words, small uncertainties (e.g. a few millimeters) can lead to underdosage in the target volume and overdosage to healthy surrounding tissue [1, 4].

Radiotherapy treatment planning is conventionally guided by single energy CT images, for tumor delineation and radiation dose calculation. Radiation dose calculation is performed on CT, mainly because the CT intensity values (Hounsfield Units (HU)) give a reliable representation of the electron densities in tissue. However, CT imaging is sub-optimal for precise and reliable tumor localization due to its limited soft-tissue contrast [5]. MR images offer better soft-tissue contrast and are therefore often additionally acquired to supplement CT images in order to improve tumor delineation [5–7]. For treatment planning

purposes, the CT and MR images have to be mapped by rigid registration which includes registration uncertainties. In conventional MR sequences there is an absence of signal from cortical bone. Because of this, and due to the inherent difference of contrast, registration of CT and MR images is difficult [3]. Additionally, the image registration might be challenged by geometric distortions, artifacts, varying patient setups and varying anatomy appearance. Furthermore, the acquisition of images from two different modalities per patient implies disadvantages due to increased costs, patient discomfort and increased workload for clinicians [8].

Another major disadvantage of the current workflow is that CT employs ionizing radiation. For most patients CT scans will be repeated weekly (or even daily) to allow for inter-fractional guidance and treatment adaption [9]. The use of CT in pediatric patients should be avoided, as the additional ionizing radiation may pose a significant risk for future development of secondary malignancies. Dismissing CT from the radiotherapy planning workflow will thus reduce radiation dose, which is also in accordance with the principle of keeping radiation dose to patients (and personnel) As Low As Reasonably Achievable (ALARA) [10].

In the treatment phase the total external dose is usually divided into several smaller doses, called fractions, to spare healthy tissue as much as possible. Compared to photon therapy, proton therapy is expected to be able to decrease radiation dose to healthy tissue even further as dose beyond the target is zero [11] or almost zero [12, 13]. Proton therapy therefore may prevent or reduce radiation induced side effects [14, 15]. Dismissing CT for image guidance in a proton therapy workflow is thus expected to be able to maximize the dose reduction to healthy tissue, preventing or highly reducing radiation induced side effects throughout the entire workflow (e.g. planning phase and treatment phase).

Due to the described limitations in the current multi-modality workflow and due to limitations of CT imaging,

there is an increased interest in developing an MR-only¹ radiotherapy treatment planning workflow. The growing enthusiasm of MR-only planning is further strengthened by the worldwide development of MR-LINAC accelerators² [16, 17]. Similar combined MR-proton therapy (MR-PT) machines are foreseen to be developed in the future. Adjustment of the workflow using MRI alone does prevent irradiation of healthy tissue for treatment planning purposes. Therefore, imaging can be repeated as often as necessary. An MR-only workflow allows for practically unlimited interfractional evaluations and adaptations of the proton therapy planning addressing uncertainties due to changes in the anatomy. It is also beneficial for the patient in terms of logistics, since only one imaging modality is required instead of two. Here we provide an overview of novel techniques that will allow for accurate (real-time) MR-only image guided proton therapy in the nearby future.

Synthetic-CT image guidance

Current status

For radiotherapy treatment planning tissue electron density information is required. In contrast to CT, no direct relationship exists between MR image intensity values and electron density values [18]. This is due to the lack of correspondence between the voxel intensity and the associated attenuation properties of the tissue in MRI [3]. This means that a method has to be available for an MRI-only workflow that is able to derive CT equivalent information from MR data.

To enable MR-only radiation treatment planning, the MR data has to be converted into maps relevant for radiotherapy planning [3]. The generated maps are generally referred to as “synthetic CT” [3], “substitute CT” [19], or “pseudo CT” [20]. In the following paragraphs the term “synthetic CT” will be used.

For the generation of synthetic CTs, several approaches can be used: voxel-based techniques, single or multi-atlas-based techniques, and hybrid techniques combining atlas- and voxel-based techniques. In the voxel-based technique the concept of machine learning is used, in which a model is trained to predict CT numbers from MRI data [3, 21]. The CT number assignment can be done on the basis of generic values to bulk groups of voxels [3, 22, 23], or by including patient-specific CT numbers in a training phase [3]. For atlas-based approaches, first a

reference dataset or atlas has to be generated based on co-registered CT and MR scans of an indication-specific patient group. For a new patient, with only an MR scan available, the location of MRI voxels can then be aligned to the location of MRI voxels in the atlas by registration. The resulting transformation is then applied to the atlas CTs to generate a synthetic CT image [3, 16]. In a hybrid approach two probability density functions (PDFs) can be calculated, for example; one based on the outcome of the atlas approach and one based on the outcome of the voxel-based approach [3]. The PDFs for each voxel can then be combined to determine the electron density value [16, 24]. Voxel-based techniques have the advantage of being able to handle patients with atypical anatomy, since they are not being reliant on an atlas [16]. Atlas based techniques, however, provide more accurate bone matches and heterogeneous HU patterns for different anatomical structures, more closely resembling real CT images [25].

Future vision

A study by Nyholm et al. [26] has shown that in prostate cancer patients systematic uncertainties can be reduced from 3–4 mm for a CT & MR workflow to 2–3 mm for an MR-only workflow, where the main contributing factor to uncertainty was the co-registration of CT with MR data. In general, the registration uncertainty introduced by registration is estimated to be in the range of 0.5 to 3.5 mm for the prostate and the brain [22, 26, 27]. As mentioned in the introduction, proton therapy is highly sensitive to spatial distortions. Voxel-based conversion of MRI data to electron density data avoids the geometric uncertainty introduced by deformable registration as used in atlas-based techniques [28].

In proton therapy the range of protons is determined from the stopping power ratio (SPR) of tissue relative to water. Calculation of electron densities from conventional single energy CT images results in an uncertainty in the SPR [29]. This is due to the degeneracy between CT numbers and SPRs, making the estimation of the SPR susceptible to variations in human tissue [30]. Recent publications have shown promising results of proton beam range calculation uncertainties with dual energy CT (DECT) to be in the order of 1% [31–33]. Therefore, it is expected that applying a voxel-based synthetic CT method on DECT data will result in less uncertainties in proton beam range calculation as compared to the conventional single energy CT based workflow.

In Figure 1 an MR-only synthetic CT approach is illustrated, where a voxel-based or hybrid technique is used to generate the synthetic CT images. In this approach, a machine learning algorithm is trained by DECT and MRI data, to predict CT values. The aim is to obtain synthetic CT data suitable for proton beam calculations purposes.

¹ The product is not commercially available. Radiotherapy where MR data is the only imaging information is ongoing research. The concepts and information presented in this article are based on research and are not commercially available. Its future availability cannot be ensured. Not for clinical use.

² The information shown herein refers to products of 3rd party manufacturer's and thus are in their regulatory responsibility. Please contact the 3rd party manufacturer for further information.

For the foreseen MR-only workflow depicted in Figure 1, MR sequences should be used that allow for bone identification to minimize uncertainties due to registration processes. Automatic voxel-based methods generally require ultra-short echo time (UTE) MR sequences [34]. One of the MR protocols that is used by Siemens Healthineers for generation of synthetic CT images is the pointwise encoding time reduction with radial acquisition (PETRA). This is a type of UTE imaging [16]. This sequence allows for fast imaging, by using Cartesian acquisition for only a few percent of the total acquisition time and radial acquisition for the remaining acquisition time [35]. This enables visualization of tissues with (ultra)short transverse relaxation times such as bone [36]. Post-processed PETRA images have been shown to have sufficient power to discriminate air from bone for the purpose of defining air masks and supporting the generation of synthetic CT from MRI data [37]. A disadvantage of a voxel-based approach is the prolonged acquisition time when multiple

sequences are used, increasing the likelihood for artefacts generated by patient motion [16]. Therefore, measures should be taken to minimize patient motion during the entire acquisition.

MR-based proton therapy planning and real-time imaging guided proton therapy

In recent years, it has been shown that for photon treatment planning absorbed dose can be accurately computed based on synthetic CT data, and that these images can also be applied as reference images for image-guided radiotherapy (IGRT) [38–40]. Recently, the first studies investigating the use of synthetic CT for proton therapy planning have also been published [41, 42]. They focus on evaluating the dose calculation accuracy for robustly optimized intensity modulated proton therapy (IMPT) when recalculated on synthetic CTs, derived via different methods. So far, these studies are limited to

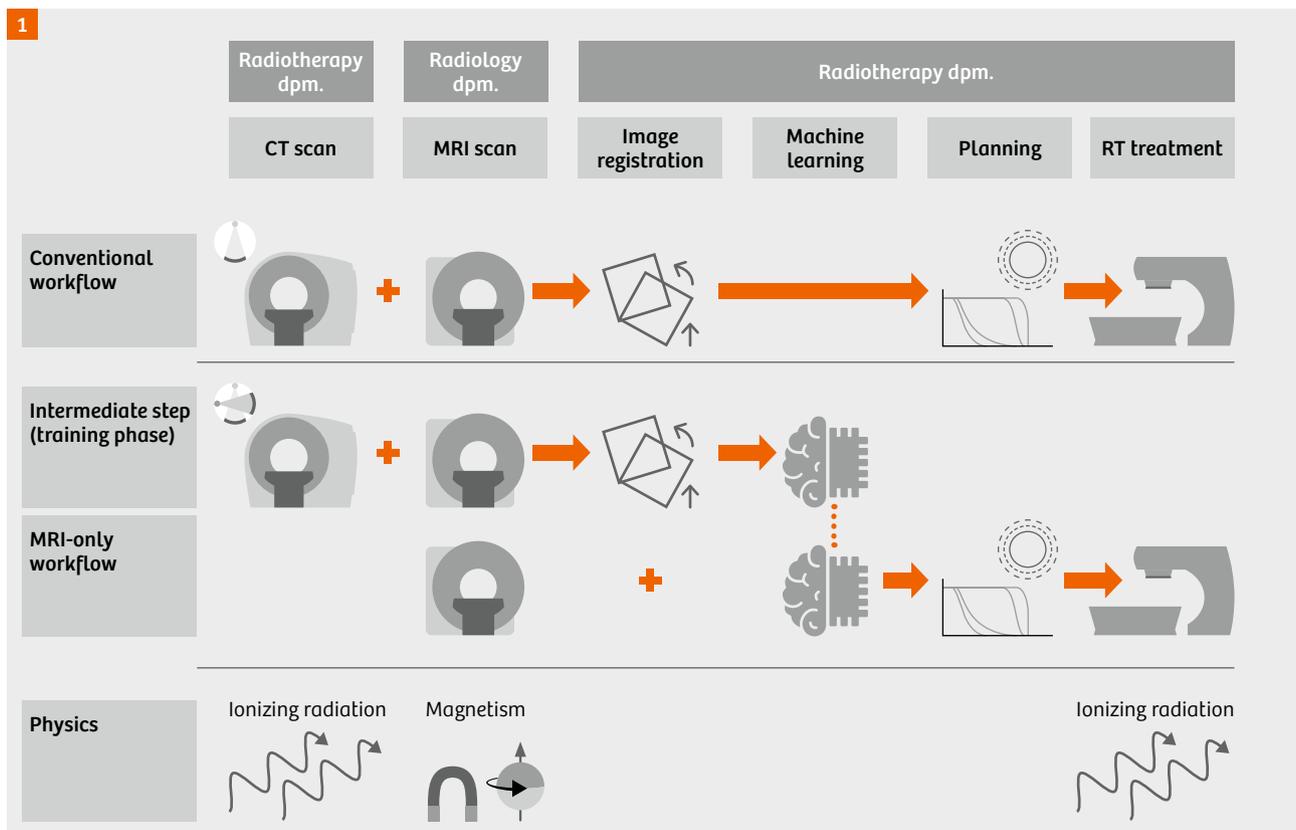


Figure 1: This figure illustrates the conventional radiotherapy workflow and an MRI-only synthetic-CT workflow. The intermediate step, that consists of employing DECT to train a voxel-based or hybrid synthetic-CT (MRI-only) model, is also shown. It is expected that this will allow for relatively accurate proton beam range calculations in the MRI-only workflow. Furthermore, the physics behind the modalities are illustrated, showing that the MRI-only synthetic-CT based workflow eliminates the ionizing radiation dose for the purpose of proton therapy planning. Abbreviation: dpm., department.

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validation cohorts of brain and prostate cancer patients. They show that for accurate MR-based proton dose calculation sophisticated synthetic CT approaches are required and that simple bulk density assignment methods are not adequate. Especially the correct modelling of internal air cavities was found to be crucial. Clinical implementation of MR-based proton therapy planning will require further investigations on the basis of considerably larger patient groups. Additionally, studies for more complex anatomical situations (where the proton beam would have to pass through considerable air or bone areas or where frequent anatomical changes are expected) are required.

In an MR-only based workflow, repeated imaging can be performed without the need for ionizing radiation, allowing for treatment monitoring and adaptation of the treatment plan on a day to day basis. Real-time MR-guided X-ray beam radiotherapy has been accomplished in combined (hybrid) MR-LINAC systems and was clinically launched in 2014 [43]. Real-time MR-guided proton therapy is receiving increased attention and is expected to be realized in the future.

Combined MR-PT machines are expected to further maximize tumor control probability and minimize radiation-related toxicity compared to real-time MR-guided photon therapy, due to the superior physical properties of the proton beam. Especially for moving tumors, real-time MR-guidance would lead to a better control of motion uncertainties and therefore improved radiotherapy treatments. Furthermore, proton beam tracking, which has always been regarded as the ultimate solution to treat moving tumors [44–47], could become clinical reality with the development of real-time MR-guided proton therapy. The concept of proton beam tracking is to dynamically steer the treatment beam and adapt its energy as a function of real-time tumor position obtained from real-time images. A synthetic CT based workflow would be the prerequisite for a real-time MR-guided proton (beam tracked) therapy treatment.

Challenges

The geometric accuracy of MR images affects the accuracy of final target volume delineation. It is limited by system-related geometric distortions arising from inhomogeneities of the static magnetic field, that increase with increasing magnetic field strength [48]. Another cause of system related geometric distortions is non-linearity of the gradient magnetic fields [48], even though manufacturers do apply non-linearity corrections to correct for this. Insight in the magnitude of those distortions and their potential impact on dose delivery can be obtained by performing a dedicated phantom study. An undistorted reference map can be generated by making a CT-scan of an MR-compatible phantom [34, 37]. Mallozzi et al. [49]

found in their phantom study that even with three-dimensional distortion correction, measurable nonlinearity can occur. In a phantom study done by Pappas et al. [48] for three clinical MR protocols, mean absolute distortions of less than 0.5 mm in any direction were found for their custom-made phantom that fits inside a head coil. However, they also found control point (total) distortions of up to 2 mm at the edges of the imaged area. In terms of image guidance for proton planning this is a considerable level of distortion. In a phantom study done by Jafar et al. [50] in which a three-dimensional printed grid phantom was used to measure spatial distortion in three dimensions for six clinical used MRI scanners, an overall mean error of less than 2 mm was found for all scanners, when using the body coil for signal acquisition. However, maximum errors above 6 mm were also detected. Although the magnitude and orientation of distortion strongly depends on imaging parameters and other influences, these kind of phantom studies do illustrate that geometric distortion has to be taken into account for proton planning purposes due to its high sensitivity to spatial distortions.

Besides being system related, geometric distortions can also be tissue related [51, 52]. Those patient-related image distortions can be minimized by using a sufficient bandwidth, for example [53, 54]. However, the bandwidth affects also the signal-to-noise ratio in the acquired images [54, 55]. Artificial Intelligence (AI) might be used to correct for geometric distortions in clinical data, based on quantification of geometric distortions in the phantom study and data obtained in the training phase in the foreseen workflow (see Figure 1). AI refers to the analysis of data with the aim of deriving a model that is used to predict and anticipate possible future events based on inferences from this model [56].

To allow for real-time MR-guided proton therapy treatment in the future, several challenges have to be overcome. Combining multiple complex technologies in one MR-PT machine requires critical evaluation of technical feasibility as mutual disturbances are introduced. For example, the magnetic field of the MR scanner will have an impact on the proton beam tracks [57, 58]. The specific geometry of an MR-PT machine might influence functional aspects of both modalities. The complex geometry of such a machine might introduce geometrical distortions in the MR images due to the magnetic field inhomogeneity [59, 60]. The proton beam arc might be limited in the choice of possible beam angles [61] as compared to standard proton therapy. Besides those modality related aspects, real-time MR-guided proton therapy also poses high demands on computational power and treatment planning capabilities. To synchronize beam delivery to the target motion real-time measurement of the target

position and real time adaptation will be required. In order to achieve that, imaging processing will have to be fast and automatic, including dose-recalculation and evaluation. In addition, decision support would need to be provided to perform the appropriate actions.

Summary

Proton therapy allows for the conforming of high radiation dose to the tumor volume, while minimizing normal tissue damage. An MR-only workflow allows for repeated imaging as MR does not involve ionizing radiation, allowing for monitoring of the treatment and an adaptation of the treatment plan with a higher frequency compared to a CT & MR based workflow. An MR-only image guided workflow also has the potential to reduce errors due to the avoidance of CT & MR co-registration.

To enable MR-only radiation treatment planning, a reliable method that converts MR data into maps relevant for radiotherapy planning is needed. This can be provided by the concept of synthetic CT. Approaches include a voxel-based or hybrid synthetic CT workflow, in which DECT data is used in the training phase, of which the value will need to be evaluated in future studies. The dose distribution in proton therapy planning is generally relatively susceptible to errors as they increase the range uncertainty of the proton beam, and therefore the use of DECT data is expected to increase accuracy of proton dose calculations. Overall the efficient and reliable generation of MR based synthetic CT images is an important prerequisite for realization of real-time MR-guided proton therapy in the future.

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