ONLINE ADAPTIVE MR-GUIDED RADIOTHERAPY

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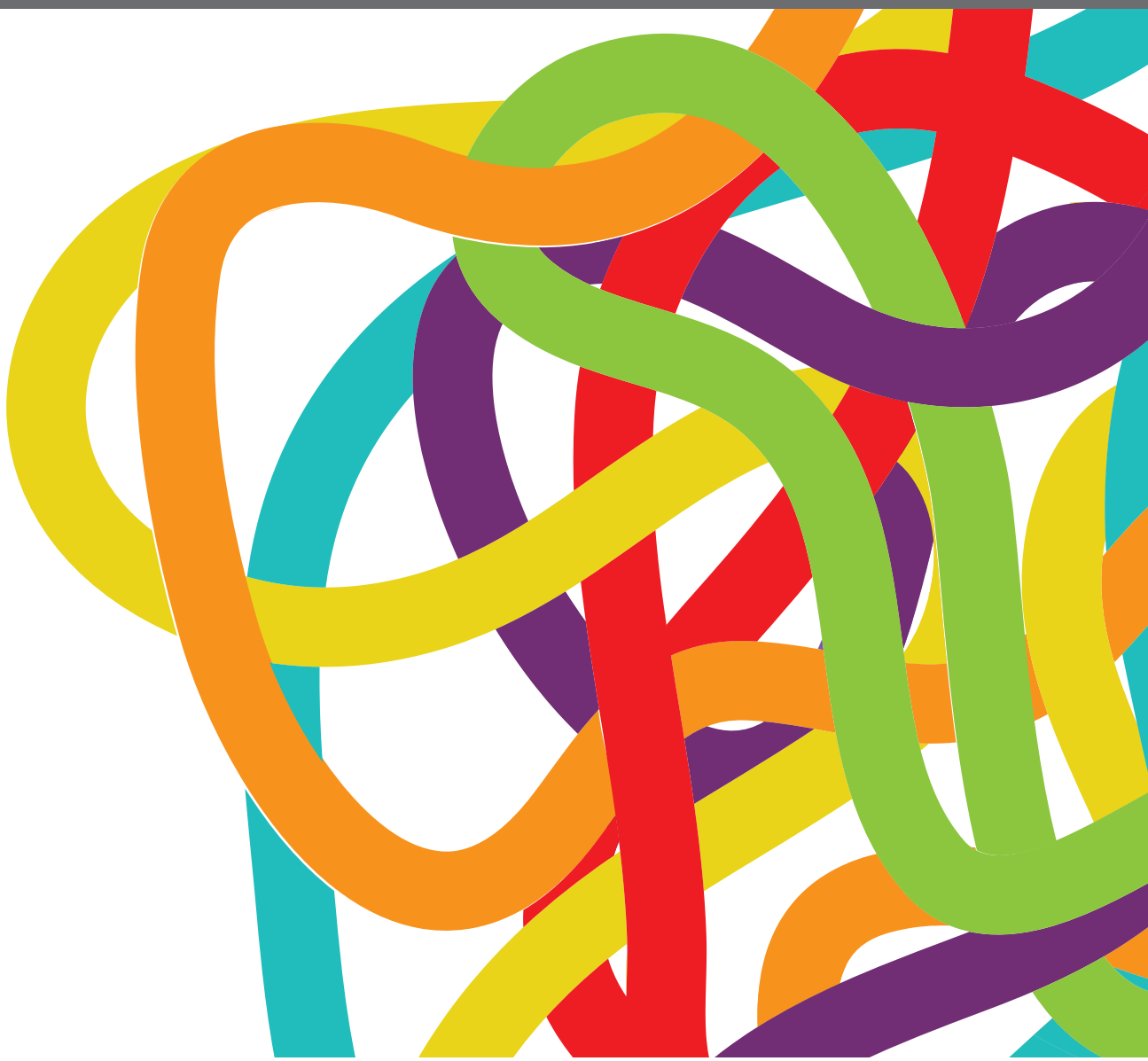

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ONLINE ADAPTIVE MR-GUIDED RADIOTHERAPY

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Table of Contents

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EDITORIAL
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Editorial: Online Adaptive MR-Guided Radiotherapy

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Editorial on the Research Topic

Online Adaptive MR-Guided Radiotherapy

The radiotherapy field is rapidly evolving due to advances in radiation delivery and image guidance. After the introduction of image guided radiotherapy (IGRT) two decades ago, the integration of magnetic resonance imaging (MRI) with linear accelerators is the next logic step in IGRT. MR-guided radiotherapy will lead to a paradigm shift in radiation oncology for multiple clinical indications in the head and neck, thorax, abdomen and pelvis and opens new opportunities to increase precision and to adapt the treatment (1–3).

In this Research Topic, the opportunities and challenges when using online adaptive MR-guided radiotherapy will be described. Online adaptive magnetic resonance guided radiotherapy (MRgRT) has the potential to improve both oncologic outcomes due to dose escalation and ultra-hypofractionation, and decrease toxicity due to improved targeting accuracy by inter- and intrafraction adaptation. However, the adaptive workflow is also time and resource intensive and requires a drastic transformation of the offline and online radiotherapy workflow (4, 5).

Two MRI linear accelerator (MR-linac) systems to deliver MRgRT are commercially available and have been clinically implemented across the world, other systems are being developed. The technical specifications, opportunities and challenges of these MRgRT platforms (Elekta Unity and Viewray MRIdian) are described by Thorwarth and Low. In order to reduce time and resources per treatment fraction, automatization of most of the realtime MRgRT workflow is necessary. Before routine implementation of these technical solutions, large standardized data sets including both clinical and technical data are required for training and clinical validation of these models.

Although differences across both platforms are present and for few indications one system may have advantages over the other, in general, both systems offer new functionality, including MR-guidance and online adaptation when compared to conventional CT-guided radiotherapy. With increasing implementation of MRgRT systems, the time window for high quality comparative (randomized) trials is narrow, as described by Verkooijen and Henke. International collaborative studies, preferably across platforms, are warranted to gain this timely evidence of the superiority of MRgRT including patient-reported endpoints. For both systems, international research consortia have been formed, where expert clinicians, physicists, methodologists, therapists and technologists join forces for an evidence-based introduction of the technology and optimize the clinical impact (6). Large international prospective data registries collecting clinical and technical data are being

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set-up aiming to include all patients treated at the MR-linac for an evidence-based introduction of the technology and further evolution of the technology (7).

When introducing complex innovations in radiation oncology, a randomized controlled trial will not be the first step after clinical implementation of the novel technology. Several preparatory steps are required before comparative studies can be initiated, especially with a continuously evolving technology and evolving clinical application. The R-IDEAL framework describes the steps towards an evidence-based introduction of the new technology, with Phase 0 (Radiotherapy predicate studies), Phase 1 (Idea, first in man study), Phase 2a (technical development studies), Phase 2b (Exploration, early effectiveness in randomized studies), Phase 3 (Assessment in comparative studies) followed by Phase 4 (Long-term results) (8). Furthermore early Health Technology Assessments of resource-intensive treatments would help facilitate the reimbursement policy.

Besides the online adaptive approach and MR-guidance during treatment, one of the unique aspects of MRgRT, is the opportunity to perform biology-based image guided adaptive radiotherapy (BIGART) as described by Van Houdt et al. By acquiring biological images revealing metabolic and functional data, focal dose escalation to the gross tumor volume within the clinical target volume can be pursued, for example for prostate cancer (9). Also this opens opportunities for 'dose painting by numbers' within the tumor volume by using the heterogenic characteristics within the tumor to deposit a differentiated dose per voxel (10). MRgRT allows for daily quantitative imaging by visualizing the tumor volume, shape and biology before and during each radiotherapy fraction. Adaptation to changing tumor shape and volume is already possible in present-day MRgRT. In addition, imaging biomarkers need to be identified that can predict treatment response early in the course of treatment, which may eventually lead to response-adapted radiotherapy. Again, large multicenter (standardized) imaging and clinical data with multicenter and multiple tumor site validation are necessary, which further strengthens the importance of collaboration in large international data registries.

While BIGART may potentially impact all radiotherapy (+/- systemic therapy) applications, it may be of particular importance for the enhancement of radio-immunotherapy. The immunogenic effect of radiation and its synergy with immunotherapy, has been observed in several pre-clinical and clinical studies and in pre-clinical studies the dose per fraction seemed to be critical (11). As MRgRT allows for safe ultra-hypofractionation and reduces the volume of normal tissue irradiated by reduced treatment margins, radio-immunotherapy delivered by MR-guidance may be a perfect match. Furthermore, MRgRT facilitates visualization of the anatomical sites that should or should not receive radiation, allowing for new clinical treatment paradigms such as partial tumor irradiation or draining lymph node sparing. Many questions need to be addressed such as radiation dose, fractionation, timing of radiotherapy versus immunotherapy, target volumes and biomarkers for response prediction as highlighted by Hörner-Rieber et al. It should not be a surprise, that international collaboration, standardization and clinical and imaging data collection, including biomaterial, will be the driving force towards optimization of this combination treatment and proving its impact on oncological outcomes.

Since 2015, MR-linacs have been first used and were implemented across the world from initial users to now dozens of early adopters (12, 13). After the predicate and first in man studies, for several clinical indications studies have been performed on the early effectiveness, toxicity and patient reported outcomes of MRgRT. In this editorial, several review articles on MRgRT to treat tumors in the brain and spine, head and neck, lung, esophagus, pancreas, kidney, liver, cervix, prostate, bladder and rectum) are presented, including an overview of the current evidence, clinical experience, state of the art implementation of MR-guided radiotherapy and future perspectives (Boldrini et al.; Boeke et al.; Tocco et al.; Crockett et al.; Boldrini et al.; Maziero et al.; Lee et al.; Hall et al.; Keller et al.; Hijab et al.; Portelance et al.).

Although clinicians see the great potential of MRgRT as a logical next step in IGRT, and the first studies support the potential benefit of MRgRT, randomized clinical evidence is not yet available. A collaborative international effort (across platforms) to set up comparative trials or prospective registry studies will be necessary in the generation of high quality evidence on the benefits of MRgRT over CT-guided radiotherapy.

With this Research Topic on online adaptive MR-guided radiotherapy, we aim to give the reader an overview of the ongoing advances in MR-guided radiotherapy to facilitate institutes on the verge of implementation of MR-guided radiotherapy into clinical practice. We thank all authors for their excellent invited reviews and their willingness to collaborate across platforms and share their expertise on MR-guided radiotherapy. We believe that MR-guided radiotherapy can have a tremendous impact on outcomes for patients for multiple oncological indications. Advances in image-guided adaptive and response-based radiotherapy are expected to translate into improved oncologic outcomes, increasing the number of indications to be treated by stereotactic radiotherapy as a non-invasive treatment modality, reducing toxicity and reducing the impact of cancer treatment on quality of life. Therefore, we would like to make a 'warm plea' for international and across platforms collaboration of experts involved in the multidisciplinary teams of MR-guided radiotherapy to maximize the benefit of this paradigm shift in radiation oncology and to prove its superior outcome and cost-utility for the radiotherapeutic treatment of cancer patients rather sooner than later.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of this editorial. LK drafted the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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MR-Guided Radiotherapy for Prostate Cancer

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External beam radiotherapy remains the primary treatment modality for localized prostate cancer. The radiobiology of prostate carcinoma lends itself to hypofractionation, with recent studies showing good outcomes with shorter treatment schedules. However, the ability to accurately deliver hypofractionated treatment is limited by current image-guided techniques. Magnetic resonance imaging is the main diagnostic tool for localized prostate cancer and its use in the therapeutic setting offers anatomical information to improve organ delineation. MR-guided radiotherapy, with daily re-planning, has shown early promise in the accurate delivery of radiotherapy. In this article, we discuss the shortcomings of current image-guidance strategies and the potential benefits and limitations of MR-guided treatment for prostate cancer. We also recount present experiences of MR-linac workflow and the opportunities afforded by this technology.

Keywords: prostate cancer, MR-linac, image-guided radiotherapy, online adaptive radiotherapy, MR-guided radiotherapy

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INTRODUCTION

Prostate cancer has accounted for 23.2% of all male cancer diagnoses in Europe in 2020 so far (1), a large proportion of whom will be treated with external beam radiotherapy (EBRT) for localized disease. EBRT offers patients non-invasive radical treatment and the move toward hypofractionation has allowed treatment schedules to be shortened. The low estimated α/β ratio of prostate cancer hypothesizes a benefit of hypofractionation, which has subsequently been evidenced in a number of trials (2–4) and transitioned into clinical practice guidelines across Europe (5–7) and America (8). Such results have encouraged clinicians to explore the boundaries of ultra-hypofractionation (UHF), testing 5 or 7 fraction schedules with promising oncological results (9–11).

Whilst the biology of prostate cancer may lend itself to hypofractionation, multiple obstacles remain in the pursuit of accurate dose delivery. Inter- and intra-fractional variability of target organ morphology and position as well as organ-at-risk (OAR) deformation limit the safety of dose escalation and hypofractionation with current image-guided radiotherapy (IGRT) techniques. The HYPO-RT-PC trial, comparing UHF for localized prostate cancer to conventional fractionation, reported significantly higher levels of patient-reported acute bowel and urinary toxicity with UHF (11), though late-term toxicity appeared equivalent regardless of treatment arm. However, these

findings were not correlated in acute toxicity findings from the PACE-B trial in which the SBRT cohort reported similar levels of acute toxicity to the standard fractionation cohort (10). These differences may be due to radiotherapy technique, underlying the importance of optimizing dose delivery. Specifically, the radiation planning technique used for 80% of patients in the HYPO-RT-PC trial was three-dimensional conformal RT, rather than the more modern intensity-modulated RT, which has been associated with lower absolute rates of toxicity (11). Additionally, more generous planning margins were placed around the prostate to mitigate uncertainties due to prostate motion. Thus, the absolute rates of toxicity in the HYPO-RT-PC trial are likely higher than would be expected with modern treatment planning and delivery. Nonetheless, toxicity remains a possibility with all techniques and this remaining toxicity is likely determined not only by intrinsic radiosensitivity but also by doses delivered to critical adjacent organs.

The use of IGRT in prostate cancer is associated with improved biochemical control and lower rates of toxicity (12–14). MR-guided radiotherapy (MRgRT) brings IGRT to a higher level with improved soft tissue contrast and online adaptive planning allowing for greater accuracy of fraction delivery. MRgRT provides the opportunity to improve cancer outcomes while reducing treatment-related toxicity. Presently, there are two commercially available systems from which current experiences are drawn: Elekta Unity (Elekta AB, Stockholm, Sweden) which uses a 1.5 Tesla MRI machine, and Viewray MRIdian MR Linacs (Viewray Inc, Oakwood, OH) which uses a 0.35 Tesla MRI (15).

In this review, we will explore the shortcomings of current IGRT methods and the potential benefit and limitations of online adaptive MRgRT in prostate cancer. We will also describe current clinician experience of MR-guided workflow and the potential opportunities for future development and trials.

SHORTCOMINGS OF CURRENT IGRT STRATEGIES

Current IGRT techniques include the use of cone-beam CT (CBCT) and implanted fiducial markers (FM), which may be used in conjunction; however, both have their limitations. CBCT alone has poor soft tissue resolution, limiting the accuracy of prostate-prostate matching (16). The use of radiopaque fiducials allows for rigid-registration but provides little to no information about organ deformation, seminal vesicle location, or bladder or rectal distension (17). The placement of fiducial markers is also an invasive procedure. Uncertainties in current IGRT strategies require larger planning margins to account for internal margin and set-up error, which can increase toxicity. Inter-fraction volumetric changes of the prostate gland have also been observed in moderate and profound hypofractionation schedules (18–20) and, with the move toward ultra-hypofractionation, direct visualization of the prostate serves to ensure dose coverage.

Any inter-fraction displacement necessitating contour repositioning is purely based on prostate matching and does not take into account the potential for differential movement of target organs such as seminal vesicles and pelvic lymph nodes (21, 22). Peng et al. analyzed 486 daily CT scans for 20 patients and found that in around 30% of fractions translational shifts were unable to adequately mitigate anatomical changes, indicating a need for online adaptive radiotherapy (ART) (23). While dosimetric coverage of the lymph node areas may be retained if bladder and rectal filling is pristinely maintained from fraction to fraction (24, 25), changes in anatomy could lead to overdosing of adjacent organs such as the small bowel. Furthermore, there is an increasing trend to dominant intraprostatic lesion boosts (26–28), which require additional accuracy in prostate matching adjustments on traditional kV planar or CBCT imaging.

Intra-fraction movement is an additional issue, which is sub-optimally mitigated by many current IGRT strategies. The prostate itself can move between image acquisition and beam on. Furthermore, bladder filling or rectal gas movement may influence target organ position by the order of a few millimeters, sufficient to affect CTV coverage. Both CT-based and MR-based analyses have demonstrated significant rates of intra-fractional motion. Calypso four-dimensional localization systems with the use of implanted electromagnetic markers showed prostate displacement of >3 mm 13.2% of the time during treatment (29). Similarly, three-dimensional cine MRI tracking of fiducials found prostate motion >2 mm in 43% scans by 5 min of treatment (30).

Any corrections to the field may be rendered inaccurate during beam on due to the aforementioned target position diversity (31–33), or otherwise clinicians must extend the planning margin to cover the expected excursion of prostate motion (34). A small number of non-MRgRT systems have intra-fraction motion solutions such as Cyberknife, which uses KV imaging tracking of fiducial seeds. During a fraction, which may take up to 45 min, fiducial seeds are tracked and adjustments to position can be made at 30–60 s intervals (35). However, systems for managing intra-fraction motion on the basis of fiducial markers require exposure to low doses of ionizing radiation.

POTENTIAL FOR BENEFIT WITH MRGRT FOR PROSTATE CANCER

MRI guidance with or without ART has multiple potential advantages in terms of improving accurate dose delivery. First, because the prostate is much better visualized on MRI images compared to CT images, prostate CTVs generated by MRI are smaller and more precise than CT-based contours (36). **Figure 1** shows an image of the prostate from Unity. Typically, radiation-therapy planning MRIs are fused to CT simulation images to aid in contouring, but the fusion itself introduces 1–2 mm of residual error. Use of an MR-only workflow will bypass these issues. Second, on-board MRI imaging will allow direct tracking of the prostate, dispensing with the need for fiducials and sparing the patient an invasive procedure. Third, as a treatment course progresses, the daily image acquisition and adaptive re-planning

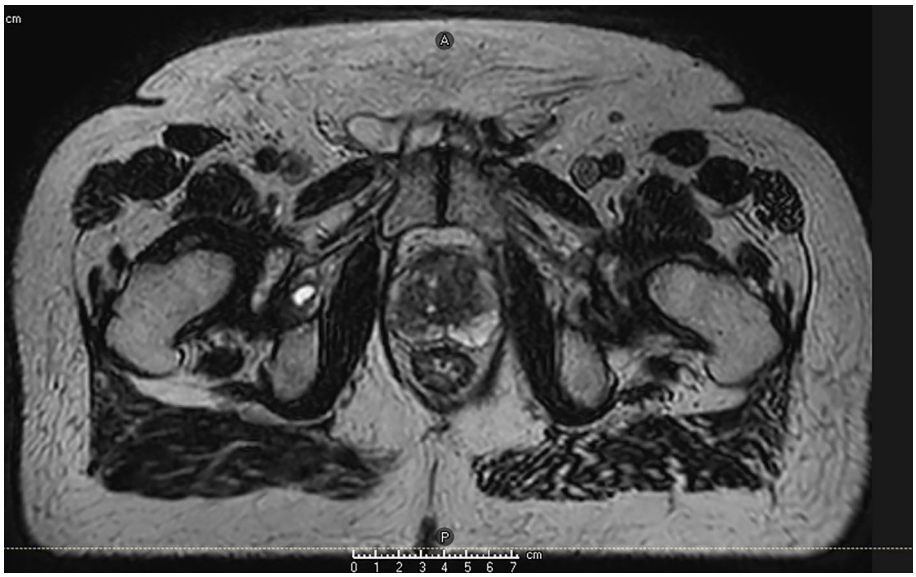

FIGURE 1 | Axial image of the prostate (T2 2 min scan) from the Unity.

allows for compensation related to prostate gland swelling, shrinkage, or deformation and inter-fractional motion of target or OARs. This daily sparing of OARs has the potential to decrease toxicity in both the short and long term. The ability to provide daily online adaptation minimizes inter-fraction uncertainty. **Figure 2** shows a daily adaptive prostate plan from a 0.35T MR-linac.

The workflow for the 1.5T MR-linac (Elekta Unity) is shown in **Figure 3** and the 0.35T MR-linac (Viewray MRIdian) in **Figure 4**. On the 0.35T MR-linac, a high resolution (1.5 mm isotropic voxel size or better) scan will be taken utilizing the on-board MRI to establish target and OAR geometry at the time of treatment. If deemed necessary, online ART with daily re-planning can be performed. During treatment, real-time imaging is acquired using MRIs obtained in a single sagittal plane at 4 frames per second, with a gating boundary on the prostate CTV at the physician's discretion. Tolerances for the proportion of the CTV outside of the gating boundary can be set, and 2-dimensional table shifts can be performed as per the physician's discretion.

For the 1.5T MR-linac, the decision to perform daily re-planning rests on review of daily anatomy alone. If anatomy has changed, re-contouring precedes a full re-optimization of the plan. The acquisition of a verification image subsequent to contouring and planning allows for there to be a shift of the new plan immediately prior to beam on (called 'Adapt-to-Position' workflow) to account for any prostate motion, which occurs during the workflow. Typically, this is due to rectal or bladder filling.

In the future, the prospect of intra-fraction dose adaptation brings us closer to the ideal online adaptive dose delivery system (37), capable of achieving the optimal balance of target dose and OAR sparing during the entirety of beam on.

CURRENT EXPERIENCE OF MRGRT IN PROSTATE CANCER

Knowledge and experience of prostate MRgRT, on both Elekta Unity and Viewray MRIdian systems, has developed rapidly in the past few years. With MRgRT presenting a revolution in RT delivery, development of workflow and assessment of patient outcomes were initial priorities. Illustrative workflows are shown for the 1.5T MR-linac (**Figure 3**) and the 0.35T MR-linac systems (**Figure 4**). Such parameters were detailed by the Amsterdam VU team who described their experiences after 700 fractions were delivered (38).

MRgRT involves a multi-disciplinary team of radiographers, physicists, and clinicians. Most global experience is with daily re-contouring and re-planning. For example, the Amsterdam team reported that 97% of their delivered fractions were online ART plans (38).

The average duration of a delivered fraction is around 45 min, during, which time the patient is required to be on the treatment couch. The Amsterdam team also reported on a number of patient-reported outcomes and found that noise was the most common complaint (38, 39). Noise may be partially mitigated by the use of noise reduction headphones, which also enables communication between patients and radiation therapists during treatment (40). Our experience to date is that patients have not had any significant problems with the treatment, and patient experience is positive (41, 42). This is echoed by other practitioners including the group at VU University Medical Center (43).

Future studies about MR-linac clinical feasibility and patient toxicity outcomes are currently underway such as the Prostate Radiotherapy Integrated with Simultaneous MRI (PRISM study, NCT03658525), and the MOMENTUM study [The Multiple

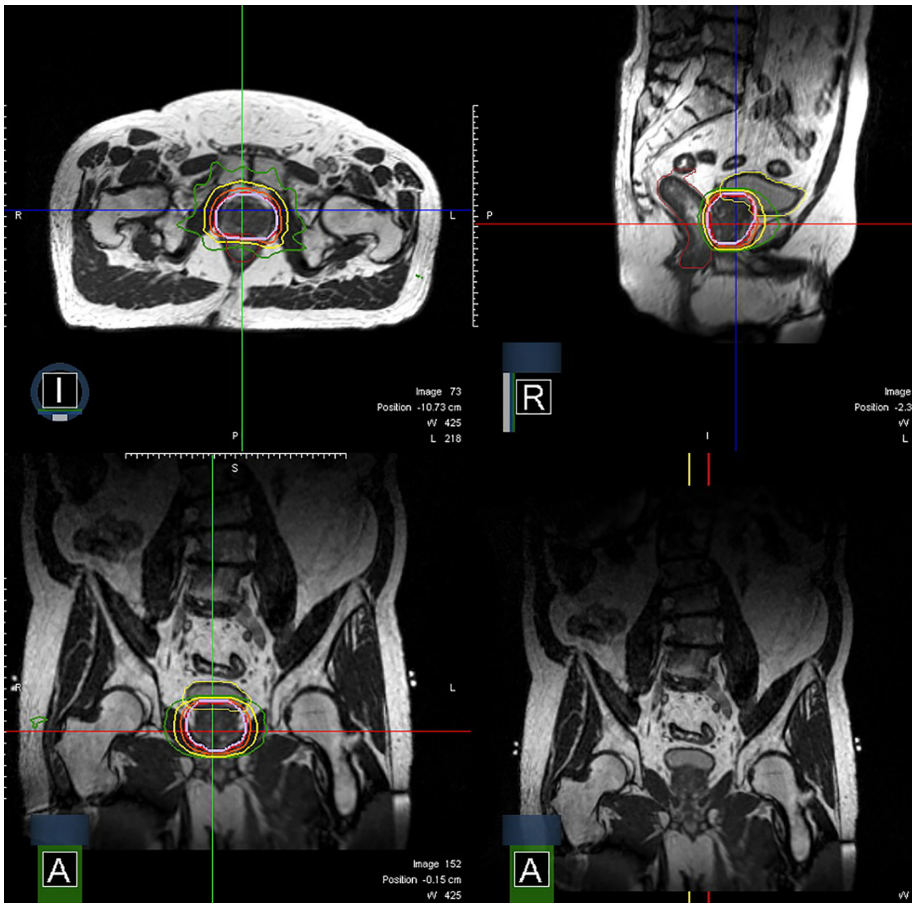

FIGURE 2 | Axial, sagittal, and coronal images of a prostate plan on the MRIdian (isodoses: Red = 40 Gy, Orange = 36 Gy, Yellow = 24 Gy, Green = 20 Gy).

Outcome Evaluation of Radiotherapy Therapy Using the MR-linac Study (NCT04075305)] (44), which will help develop faster, more efficient workflows and benchmark multi-center patient outcomes. The ongoing Magnetic Resonance Imaging-Guided Stereotactic Body Radiotherapy for Prostate Cancer trial (MIRAGE trial, NCT04384770) is a phase III randomized study comparing standard CT-guided SBRT versus MRI-guided SBRT, with the primary endpoint of acute grade ≥2 genitourinary (GU) toxicity. It is designed as a superiority study, and secondary endpoints include patient-reported outcomes and late toxicity.

PUBLISHED LITERATURE ON PROSTATE MRGRT

Outcomes for prostate radiotherapy are expected to be good for most patients, with generally low levels of side effects and high expectations of efficacy. For these patients, the benefit of MRgRT will be hard to show. However, small or marginal gains will have a high population effect due to the number of prostate cancer patients and the high likelihood of cure. There is a subset of patients with challenging anatomy where inferior dose distributions have to be accepted to preserve OAR integrity. Dosimetric improvement over a course of 20 fractions has been shown, with the number of fractions achieving all target dosimetric goals being 86% for MRgRT and 80% for simulated conventional IGRT (45). For one patient with exceptionally challenging anatomy, the prostate CTV D98% delivered was 54.5 Gy with MRgRT and would have been 49.9 Gy with conventional techniques over 20 fractions. Therefore, even though reductions in bowel and bladder toxicity will be challenging to show on a population level, this technology could meaningfully impact quality of life in those who will live for many years after cure.

Small clinical series describing experiences with MRgRT for prostate cancer have been published previously and provided detailed suggestions about the proposed benefits, challenges, and future development in this cancer type (46–48). To date, only one prospective study has published outcomes. Bruynzeel et al. (39) published early toxicity results from a phase II study on MRg-SBRT for localized prostate cancer, which reported on

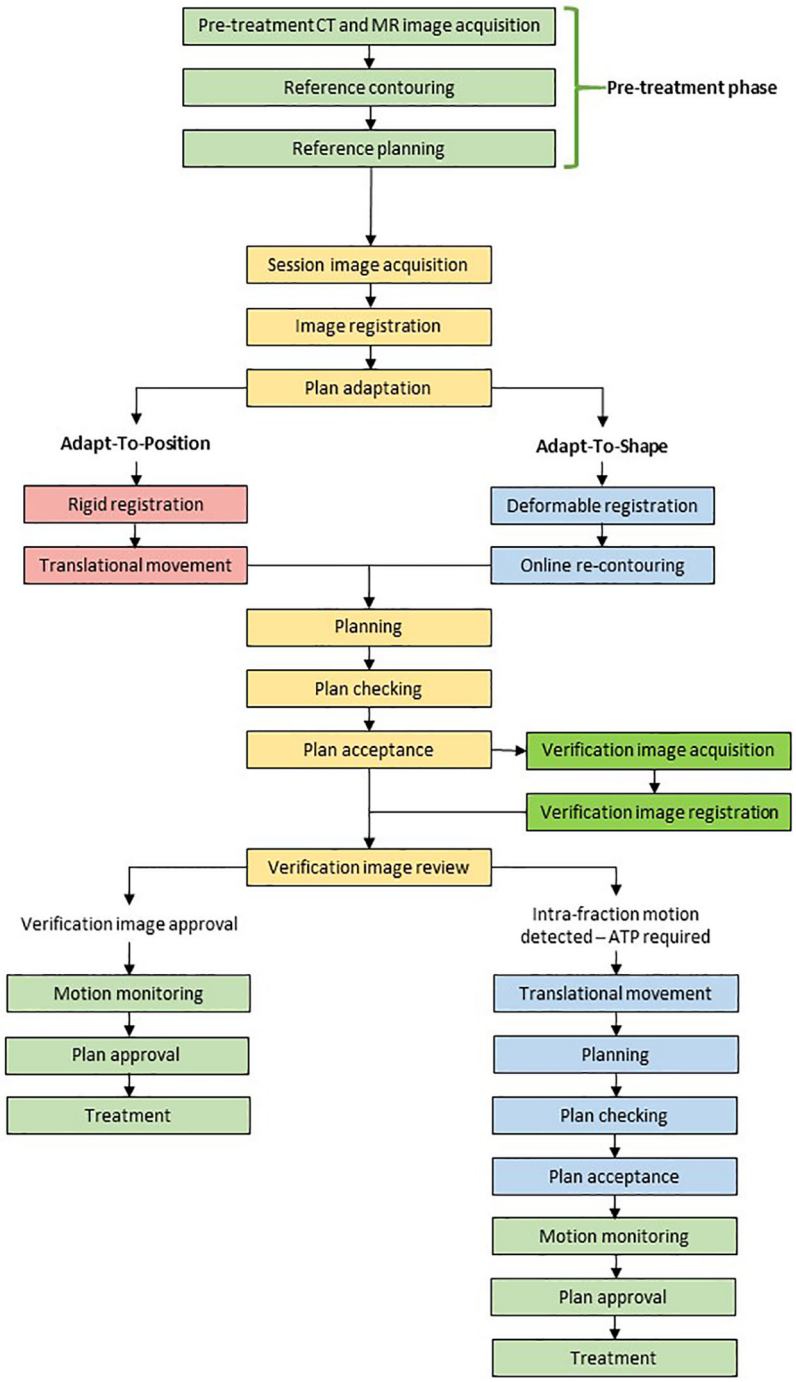

FIGURE 3 | Example workflow for the Unity.

RTOG and CTCAE clinician-reported and patient-reported outcomes (PROMs) for 101 patients for 3 months post-treatment with 36.25 Gy in 5 fractions. Clinician-reported outcomes suggested early GI and GU toxicity peaked at the final fraction of treatment and no grade 3 or higher toxicities were reported. The rates of grade ≥2 early GU and GI toxicities at the end of the treatment were 19.8% and 3%, respectively. The maximum cumulative grade ≥2 early GU and GI toxicity (by 12 weeks) measured by any symptom at any study time point was 23.8% and 5.0%. Patient-reported outcomes correlated closely

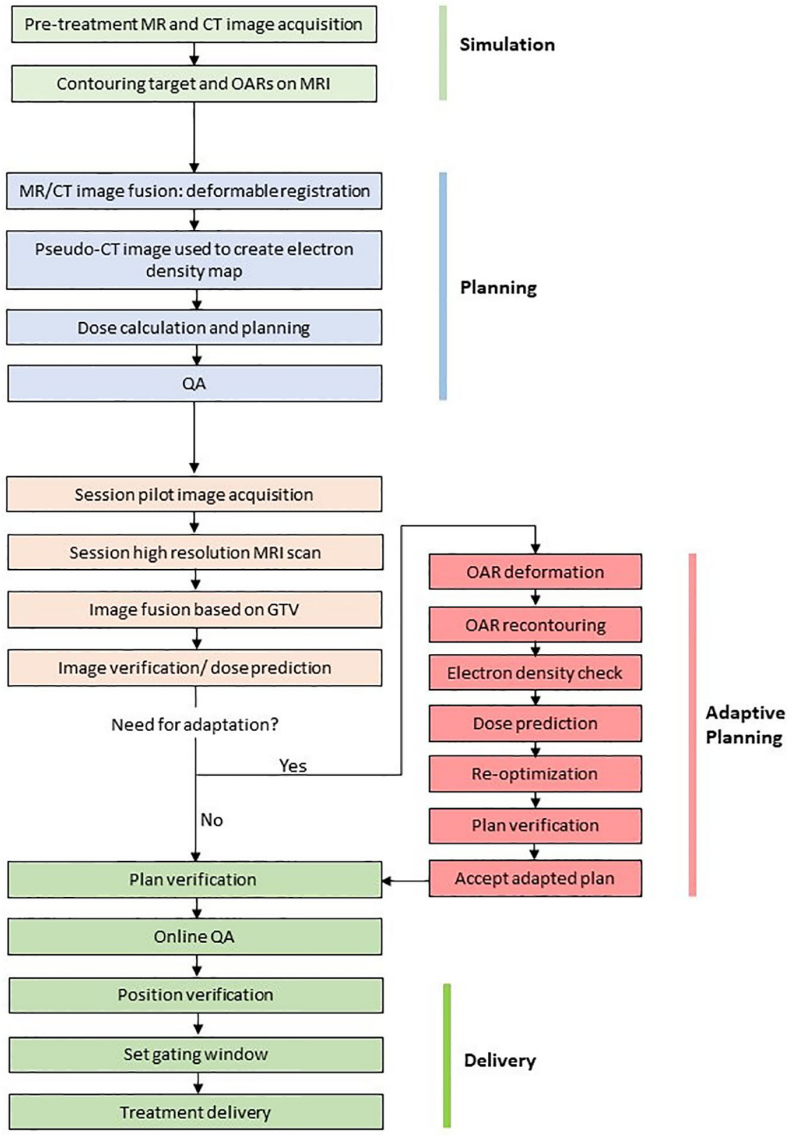

FIGURE 4 | Example workflow for the MRIdian.

with clinician reported outcomes with urinary toxicity peaking at the end of treatment and resolving by 3 months. The most common GI symptom was bloating. As a comparison to the above study, the PACE-B trial (10) showed a cumulative (exceeding baseline) CTCAE grade ≥2 GU and GI toxicity of 27.4% and 15.3% in the 5-fraction arm.

Tetar et al. (49) recently provided an update on the VU series with toxicity information extending through one year of follow-up. No grade 3 or higher toxicities were reported. All symptoms returned to baseline by 12 months. International prostate symptom scores (IPSS) returned to baseline 6 months post-treatment. 2.2% of patients reported GI symptoms at 1 year follow-up. Follow-up is too short to evaluate oncologic efficacy.

It is too early to form robust toxicity comparisons between MRgRT and non-MRgRT SBRT trials, but outcomes encourage further prospective and long-term trials to interrogate this important point.

LIMITATIONS OF MRGRT FOR PROSTATE CANCER

There are limitations to MRgRT for prostate cancer. The process of MRgRT provides a significant paradigm shift in the operation of radiotherapy departments, which necessitates updated safety training for staff, including all aspects of MR safety. Online ART

requires the attention of several staff members for each treatment, often including a radiation oncologist, multiple radiographers and a physicist. Obviously, the person-hours required to deliver MRgRT are currently high when compared to traditional linac treatment, however efficiencies are likely to be forthcoming over time.

From a logistical point of view, there is limited availability of MR-linac machines and, as a result, clinician familiarity with such systems and online adaptive planning is still progressing. The predominance of radiation oncology experience until now has been centered on CT imaging and therefore the nuances and technicalities of MRI imaging are still being learned.

Maximum field size with 1.5T MR-linac machines could also lead to limitations of therapeutic capabilities and application in node-positive prostate cancer patients. With the current Unity maximum field size of 22cm in the superior-inferior (SI) plane, it is estimated that 80% of plans across cancer types would be suitable for MR-linac treatment (50) but a significant proportion of pelvic nodal irradiation fields would be too large. With the MRIdian Linac, the maximum field size is 24 cm SI, so a similar limitation applies. However, technical solutions to this limitation, and others, are being explored and current treatment possibilities do not represent the likely full capability of MR-linac machines (51). With prostate cancer predominantly affecting those over the age of 50, there is also likely to be a greater prevalence of medical contraindications to treatment on the MR-linac, thereby reducing numbers of suitable patients. From the patient perspective, the significantly longer time on the couch may deter some, and requires greater attention to patient comfort during treatment.

One element, which could reduce workload in the future of online ART, is automation of multiple components of the workflow. Auto-segmentation has been investigated and shown to decrease inter-observer variability while increasing dosimetric consistency on CT imaging (52, 53). This was replicated in MR-guided auto-delineation of pelvic organs although there has been evidence of poor concordance of auto-segmentation for targets such as seminal vesicles and the prostate (54–56). The creation of a library of contours and atlases from which an automated algorithm can learn will likely improve outcomes further. Currently, auto-generated contours are available for clinicians on both the 0.35T and 1.5T MR-linac machines and allow for a "warm-start contour" (i.e., not starting from scratch).

The duration of fraction delivery could also be aided by auto-segmentation. As mentioned, average duration of a single fraction for prostate cancer is around 45 min and this inevitably leads to greater bladder filling and variability of rectal distension, which have been shown to affect volume and position of the prostate and seminal vesicles to independent degrees (57). Current experiences are that intra-fraction OAR variation has not resulted in a significant number of adaptations required during beam on, although further published literature is required to confirm this. The role of auto-segmentation could reduce fraction duration and thereby minimize possible compromises to target organ dose delivery.

Another limitation of MRgRT is the risk of over-intervention with MRI imaging. The session MR image acquired at the beginning of each day's treatment is a snapshot in time and one may devise a new plan based on that particular image with compromise of PTV coverage due to proximity of an OAR (e.g., bowel). OARs may move intra-fractionally (e.g., bowel peristalsis) and therefore may have unnecessarily compromised target coverage for that day.

OPPORTUNITIES FOR FUTURE DEVELOPMENT OF MRGRT IN PROSTATE CANCER

While MRgRT provides hope for safe and effective dose delivery in prostate cancer treatment, further clinical studies are required to demonstrate a benefit.

Development of an MR-only, online workflow, without pre-treatment planning, would help to decrease radiotherapy pathway duration. Dispensing of the requirement for pre-treatment procedures, such as planning scans, would allow departments to condense pathways to benefit both clinicians and patients although acquisition of pre-treatment reference plans remains the standard in MR-only workflows currently (58). Removing the requirement to fuse planning CT to planning MRI would remove a potential source of error and uncertainty in the pathway. Although CT-based electron density calculations are considered to be the gold standard for radiotherapy planning, there are commercial MR-only solutions currently available, which may become more widely used (59).

Presently, operation of MRgRT requires a significant number of person-hours. Further streamlining of session times would be likely to result from incorporating auto-segmentation, as re-contouring is the most time-consuming component of the daily workflow. It remains to be seen if the accuracy of auto-delineation ever meets the standard set forth by radiation oncologists.

Amalgamation of roles within the inter-professional team may also reduce person-hours for treatment delivery. Inter-observer variation of MR contouring has shown good concordance (60) and is sure to lead to an evolution of roles within the MR-linac team starting with high volume, low complexity cases, which may become radiographer-led.

The predominant areas of opportunity lie within extreme hypofractionation in the online ART setting. Within the field of primary treatment of localized prostate cancer, ultra-hypofractionated SBRT schedules have been shown to be non-inferior to conventionally fractionated schedules (11). The increased levels of acute toxicity in the HYPO-RT-PC trial (11), and the lack of this in the PACE B trial (10), underline the importance of technical iteration to improve patient outcomes. Further studies to compare SBRT on traditional linac compared to MR-linac are under way, including the aforementioned phase III MIRAGE trial.

Many studies are undergoing to investigate possible superiority of dominant intraprostatic lesion (DIL) boosts (27). Doses of over 90 Gy equivalency have been shown to be safe (61, 62) but, as discussed above, our current IGRT strategies are imperfect for adapting to daily anatomical changes. Online ART

using a 1.5T MR-linac would allow direct visualization of DILs during treatment. This is achievable on 1.5 T MR-linacs with diffusion scanning capabilities but, at present, 0.35T machines do not provide sufficient resolution to visualize DILs. Therefore rigid propagation is one option for this technique on a 0.35T MR-linac but alternative techniques to improve primary tumor visibility may be required; these have been employed in the diagnostic MR setting (63) but not as of yet in the therapeutic field. The feasibility of DIL visualization is also decreased with concomitant androgen deprivation therapy (62).

Other opportunities, beyond the scope of this review, include the use of MRgRT for post-operative prostatic bed irradiation or re-irradiation for radio-recurrent disease. The ability to provide more accurate dose-escalated treatment with direct visualization of tumor bulk has implications for post-prostatectomy relapses. The RADICALS-RT trial recently reported its 5 year results, which showed non-inferiority of salvage radiotherapy compared to adjuvant treatment (64). Currently, standard of practice is to treat the prostate bed empirically upon biochemical failure. The use of multi-parametric MRI (mpMRI) has been shown to be of use in detection of locally recurrent disease (65, 66); those with macroscopic disease on MRI could be triaged to treatment on the MR-linac with the possibility of macroscopic lesion boost (67, 68). In addition, as larger margins and a formulaic derivation of the target volume is currently used for prostate bed treatments, there is the prospect of reducing toxicity with MRgRT—one current phase II study promises to shed light on the efficacy and toxicity of MR-guided SBRT and CT-based SBRT delivered in the post-prostatectomy setting (NCT03541850). There are also few salvage treatments for locoregional recurrent disease after radical prostate EBRT. Early toxicity results of re-irradiation salvage SBRT are favourable (68–70) and further research into MR-guided salvage re-irradiation may be useful.

Qualitative and quantitative inter-fraction assessment of tumor response with functional MRI has implications for future treatment (71). The ability to directly visualize biological response to radiotherapy during a treatment course would allow the opportunity to tailor dose delivery. Online daily ART to target areas of persistent areas of restricted diffusion, for example, could possibly improve outcomes although implementation of functional imaging on MR-linac poses a number of challenges (72). For instance, there is a decrease in signal intensity of healthy prostate tissue on T2-weighted imaging during the course of treatment, which reduces visibility of the dominant intraprostatic lesion (73).

Thanks to the persistent and focused efforts of many prostate radiotherapy researchers over the last decade, significant GI and GU side effects of radiotherapy are becoming rarer. Effects of radiotherapy on sexual function are now the most prevalent long term side effect experienced by patients. The structures, which require dosimetric sparing in order to preserve sexual function, are not well elucidated, but it is thought that this is vascularly-mediated. Excellent outcomes have been seen after sparing the internal pudendal artery (74) using standard image-guidance strategies. As the vascular structures can be clearly seen on the MR-linac, it may be possible to preserve sexual function by sparing visualized vessels. Further study is planned.

As we progressively hypofractionate in prostate cancer, optimising image-guidance becomes ever-more important. Research is currently planned to investigate reducing the number of fractions below 5, to explore the limits of hypofractionation. The ONE SHOT trial aims to assess the efficacy of a 19 Gy fraction with 17Gy urethral sparing with a 2 mm margin. No grade 3 or higher GU and no grade 2 or higher GI toxicities were observed (75), although current HDR brachytherapy data suggests that a single fraction may be sub-optimal (76). Two-fraction HDR appears to have excellent outcomes and the MR-linac would be the perfect EBRT platform to test this in prostate cancer.

CONCLUSIONS

MRgRT presents a new paradigm shift in the delivery of prostate radiotherapy. Increasing accuracy of delivery and promising early experience will further encourage larger investigations of the benefit of MRgRT. The use of MRgRT could abolish the requirement for pre-planning and lead to shorter pathways, potentially with improved outcomes. Cohort randomized trials are needed and these will require collaboration between industry and academic partners to provide robust evidence for practice.

AUTHOR CONTRIBUTIONS

BT composed the original draft and was responsible for incorporating alterations and produced a figure. AK, TM, and AT contributed figures and critically appraised the article. LK critically appraised the article. All authors contributed to the article and approved the submitted version.

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Quantitative Magnetic Resonance Imaging for Biological Image-Guided Adaptive Radiotherapy

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MRI-guided radiotherapy systems have the potential to bring two important concepts in modern radiotherapy together: adaptive radiotherapy and biological targeting. Based on frequent anatomical and functional imaging, monitoring the changes that occur in volume, shape as well as biological characteristics, a treatment plan can be updated regularly to accommodate the observed treatment response. For this purpose, quantitative imaging biomarkers need to be identified that show changes early during treatment and predict treatment outcome. This review provides an overview of the current evidence on quantitative MRI measurements during radiotherapy and their potential as an imaging biomarker on MRI-guided radiotherapy systems.

Keywords: quantitative magnetic resonance imaging (MRI), biological image-guided adaptive radiotherapy, magnetic resonance imaging (MRI)-guided radiotherapy, functional magnetic resonance imaging (MRI), treatment response

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INTRODUCTION

At the turn of the century, two novel concepts were introduced in radiation oncology that acknowledged the complexity of tumor biology and that presented the challenges that must be met to improve the outcome of radiotherapy. Recognizing that tumors can respond rapidly to fractionated treatment, Yan et al. introduced the concept of adaptive radiation therapy (1). Instead of delivering the entire treatment with a single treatment plan based on pre-treatment imaging, the proposal was to create a closed-loop process where the treatment plan could be modified based on observed changes in the patient. To date, with state-of-the-art linear accelerators, on-board imaging equipment and software for image processing and treatment planning, we see this concept come to fruition (2, 3). The second concept, introduced by Ling et al., addressed the biological heterogeneity of a tumor (4). Using biological images that reveal metabolic, functional, physiological, genotypic, and phenotypic data, a biological target volume could be defined. This could be used to 'paint' a dose distribution that matched the biological heterogeneity. Since then, many imaging biomarker studies have been conducted, essentially trying to establish how radiosensitivity can be visualized non-invasively (5). It was shown that while tumors indeed are quite heterogeneous, this heterogeneity changes during the course of fractionated radiotherapy (6, 7).

At this stage, it becomes clear that, considering the biological characteristics of the tumor as well as its dynamic nature during treatment, the two concepts of biological targeting and adaptive radiotherapy need to be merged. Based on frequent imaging, monitoring the changes that occur in volume, shape as well as biological characteristics, a treatment plan can be updated regularly to

accommodate the observed response (8). While the logistical challenges for biological image-guided adaptive radiotherapy (BIGART) made the concept almost infeasible to carry out in practice, the emergence of MRI-guided radiotherapy (MRIgRT) platforms may be a game changer (9, 10).

For this purpose, imaging biomarkers need to be identified that show changes early during treatment and predict treatment outcome. Quantitative MRI (qMRI) techniques can be used to assess tumor morphology, biology and function. Therefore, they are promising imaging biomarkers for BIGART (9). In this review, we summarize the current evidence on repeated qMRI measurements during radiotherapy and the potential for such an approach with MRIgRT systems.

QUANTITATIVE MANETIC RESONANCE IMAGING BIOMARKERS

The majority of MRI biomarker studies investigate the potential of a measurement prior to the onset of treatment to predict outcome (11–13). In addition, promising evidence has emerged showing changes in qMRI values during radiotherapy. This suggests that qMRI parameters are prognostic for outcome and might be potential biomarkers for BIGART (9). In this section the literature is discussed in which measurements during the course of radiotherapy were reported (**Table 1**). Studies with only pre- and post-treatment measurements were out of the scope of this review.

Diffusion weighted imaging (DWI) has been the most investigated technique so far. The apparent diffusion coefficient (ADC) derived from DWI data has been associated with the cell density of the tissue. Radiotherapy results in breakdown of cellular membranes and finally necrosis (13, 100). As a result the cell density is reduced, which will be observed as an increase in ADC. For many tumor sites, changes in ADC parameters early during radiotherapy have been reported, including rectal cancer (14–20), cervical cancer (26–38), head and neck cancer (40–47), esophageal cancer (49–56), brain cancer (58), lung cancer (59), and liver cancer (60). The majority of the studies report a larger increase in average ADC values for responders compared to

TABLE 1 | Summary of MR imaging techniques for which changes during the course of radiotherapy have been investigated.

MR imaging technique	qMRI metric	Tissue characteristics	Studies investigating changes during RT
DWI	ADC	Tissue cell density	Rectum (14–25) Cervix (26–39) Head-and-neck (40–48) Esophagus (49–57) Brain (58) Lung (59) Liver (60) Prostate (61, 62) Sarcoma (48)
DCE-MRI	semi-quantitative measurements (e.g. peak enhancement) quantitative parameters derived with pharmacokinetic modeling (e.g. K^{trans}, v_e)	Perfusion and vascular permeability of tumor microenvironment	Cervix (32, 63–65) Head-and-neck (44, 66, 67) Esophagus (50) Liver (68)
IVIM	f, D, D*	Tissue perfusion and cell density	Cervix (69–74) Esophagus (75, 76) Head-and-neck (77, 78) Brain (79, 80)
Relaxometry	T2, T1, PD, T2*	Tissue relaxation times	Prostate (61, 62) Brain (81, 82)
Spectroscopy	e.g. choline to creatine ratio	Metabolism	Brain (83–86) Cervix (35) Head-and-neck (87)
OE-MRI	O_2 concentration	Hypoxia	Lung (88)
Saturation transfer MRI (MT, CEST)	e.g. MTR, qMT, MTR_{asym}, MTR_{amide}	Tissue macromolecular content (e.g. lipids, proteins, peptides)	Brain (81, 89, 90) Head-and-neck (91)
Fat composition	PDFF, %PDFF	Fat content	Bone marrow (92)
Radiomics	Histogram features, local textural features	Tissue heterogeneity	Cervix (93, 94) Rectum (95, 96) Head-and-neck (97) Sarcoma (98) Pancreas (99)

Papers were searched on PubMed with search terms "early response" and "radiotherapy" or "radiation oncology" as well as measurements during treatment mentioned in title or abstract. Only studies in humans and in English were included. Reference list of the included papers were checked to identify other relevant papers.

DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; DCE-MRI, dynamic contrast-enhanced MRI; K^{trans}, volume transfer constant between blood plasma and extravascular extracellular space; v_e, fractional volume of extravascular extracellular space; IVIM, intravoxel incoherent motion imaging; f, perfusion fraction; D, diffusion coefficient; D, pseudo-diffusion coefficient; T2, T2 relaxation time mapping; T1, T1 relaxation time mapping; PD, proton density mapping; R2*, R2* mapping; OE-MRI, oxygen-enhanced MRI; MT, magnetization transfer; CEST, chemical exchange saturation transfer; MTR, magnetization transfer ratio; qMT, quantitative magnetization transfer; MTR_{asym}, magnetization transfer asymmetry; MTR_{amide}, magnetization transfer ratio of amide protons; PDFF, proton density fat fraction.*

non-responders (15–20, 29, 33, 36, 41, 44–47, 49, 51, 54–56, 60). Some studies observed a significant increase for responders and not for non-responders (14, 35, 43). Only a few studies did not observe a significant difference in the changes in ADC values between responders and non-responders (34, 52). For example, in a study with 108 cervical cancer patients there was no difference in the increase in ADC values between complete and partial responders (34).

Dynamic contrast-enhanced (DCE-) MRI indirectly measures the tissue perfusion and vascular permeability of the tumor microenvironment and has been proposed as a biomarker for radiotherapy (101, 102). The enhancement reflects the abnormal microvasculature in tumors (102). Changes during treatment in DCE-MRI have been investigated to a lesser extent than DWI. Most studies have been performed for cervical cancer (32, 63–65). One of the first studies showed with a semi-quantitative analysis that an increase in enhancement early during treatment was predictive for local recurrence (63). Gong et al. observed similar results, as they found a significant relation between the change in mean enhancement and tumor regression rate (64). This was confirmed in a larger patient population showing that patients with an improved perfusion during treatment have a more favorable outcome (65). Quantitative analysis of DCE-MRI data showed an increase in K^{trans} (volume transfer constant between blood plasma and extravascular extracellular space) and v_e (fractional volume of extravascular extracellular space) during treatment, both in week 1 and week 4 (32). K^{trans} decreased 1 month after treatment again. The changes in K^{trans} and v_e during treatment were not correlated to changes in tumor volume. In a small group of head and neck cancer patients a larger increase in K^{trans} and v_e was observed in responders than in non-responders (44). Similarly Baer et al. reported that changes in K^{trans} and the area under the curve were predictive for survival (66). In addition, patients that have large persistent subvolumes with low blood volume within the primary tumor have a higher probability of local failure (67). For esophageal cancer, a decrease in K^{trans} was reported in complete responders (50). For liver metastases, an increase in slope and peak at week 2 was associated with an improved local response (68).

A limitation of DCE is that contrast agent needs to be injected intravenously. This could present logistical challenges and might not be amenable for repeated imaging. Alternatively, intravoxel incoherent motion (IVIM), based on multi-b-value diffusion, has been investigated for probing microscopic perfusion (103). By modeling the diffusion data with a perfusion component that predominantly affects low b-value data, a surrogate for tissue perfusion can be calculated (104). Studies in cervical cancer have reported changes in IVIM parameters during treatment (69–74). The perfusion fraction (f) first increased early during treatment and decreased later during treatment (72). Early increases in f have been associated with good response (70, 73). In esophageal cancers, responders showed a larger mid-treatment increase in the diffusion coefficient (D) of the tumor compared to non-responders (75, 76). Head-and-neck cancer patients with regional failure showed higher D values and larger reductions in f than patients with regional control (77).

For other qMRI techniques changes during treatment have been investigated only on a small scale so far. Spectroscopy has mainly been applied in brain (83–86). Changes in choline and lactate metrics during treatment were significantly related to outcome in patients with glioblastoma (83) and glioma (84). In two other studies only changes after treatment were significantly related to outcome (85, 86). For cervical cancer, changes in choline metrics could not predict treatment outcome (35). For head-and-neck cancer, choline metrics were stable in the first two weeks of treatment in responders and non-responders (87). Magnetization transfer (MT) and chemical exchange saturation transfer imaging (CEST) can be used to characterize the macromolecular content of tissue (105, 106). Changes during treatment have been investigated in glioblastoma (81, 89, 90) and head-and-neck cancer (91). All studies demonstrate the promising value of MT or CEST parameters as possible biomarkers for BIGART. Another promising technique is oxygen-enhanced MRI requiring an oxygen challenge (107). This technique was used in lung cancer patients to assess the hypoxic volume in the tumor (88). In the second week of the treatment the hypoxic volume was smaller than before treatment. Fat quantification could be useful to assess changes in tissue composition. For example, changes in fat fraction were correlated with changes in bone marrow composition induced by radiotherapy (92), which could be useful to assess hematologic toxicity. A few studies have looked into the potential of radiomics, where textural features derived from anatomical or functional images were tested (93–95, 97). Recently, deep learning approaches have been applied to extract information from images during treatment for response prediction (95, 108).

The evidence so far is mostly based on one or two measurements during treatment. Only a few studies used more than two measurements during treatment (**Table 2**). The study of Sun et al. showed in a population with mixed tumor sites that changes in ADC were correlated with treatment response and independent of tumor location (21). After the first week of treatment significant differences between responders and non-responders were observed, while a change in tumor size was not visible that early. In a study with cervical cancer patients, measurement of ADC at two weeks seemed optimal for monitoring early treatment response (39). Similar results were found for esophageal cancer (57) and rectal cancer (22). In contrast, a study with nine rectal cancer patients reported a decrease in ADC from week 2 onwards (23). Two studies investigated weekly changes in T2 and ADC values during treatment of prostate cancer (61, 62). While there were differences in overall treatment duration between the two studies, both studies did not observe early changes in either T2 or ADC. Only late ADC changes for the tumor were observed. However, the relation with treatment outcome was not assessed. A study in head-and-neck cancer patients investigated whether changes in IVIM parameters were visible during treatment (78). They showed a significant increase in ADC and D during treatment for patients with complete response. No significant differences were observed for the other IVIM parameters in the complete responding or non-responding patients.

TABLE 2 | Overview of studies with more than two measurements during treatment.

Paper	MRI Technique	Tumor site	No. patients	No. time points
Diagnostic scanners				
Sun et al. (21)	DWI	Lung, esophagus, gastric, rectum, and liver metastases	102	Pre, w1, w3, w6 or pre, w1, w2, w4
Liu et al. (39)	DWI	Cervix	33	Pre, d3, d7, d14, 1m, and post
Wang et al. (57)	DWI	Esophagus	38	Pre, weekly (6x)
Cai et al. (22)	DWI	Rectum	15	Pre, weekly (5x)
Hein et al. (23)	DWI	Rectum	9	Pre, weekly (4x)
Foltz et al. (61)	DWI, T2	Prostate	17	Pre, w2, w4, w6, w8
Van Schie et al. (62)	DWI, T2	Prostate	47	Pre, every fraction (5x)
Paudyal et al. (78)	IVIM	Head-and-neck	34	Pre, weekly (3x)
Mahmood et al. (79)	IVIM	Brain metastases	29	Pre, every fraction (10x), post
Mahmood et al. (80)	DWI	Brain metastases	21	Pre, every fraction (10x), post
Bostel et al. (24)	DWI	Rectum	8	Every fraction (28x)
MRIgRT systems				
Yang et al. (48)	DWI	Head-and-neck, sarcoma	6	Pre, every 2-5 fractions (4-7x)
Shaverdian et al. (25)	DWI	Rectum	3	Every 3-7 fractions (4-7x)
Nejad-Davarani et al. (82)	T1, PD, R2*	Brain metastases	4	Pre, weekly (7x), post
Gao et al. (98)	DWI	Sarcoma	30	Fraction 1, 3, and 5
Boldrini et al. (96)	T2*/T1*-weighted	Rectum	16	Pre, weekly (5x)
Simpson et al. (99)	T2*/T1-weighted	Pancreas	20	Every fraction (5x)

Papers were searched on PubMed with search terms "early response" and "radiotherapy" or "radiation oncology" as well as measurements during treatment mentioned in title or abstract. Only studies in humans and in English were included. Reference list of the included papers were checked to identify other relevant papers. From those only papers with more than two measurements during treatment are presented in this table. Pre, pre-treatment; d, day; w, week; m, month; post, post-treatment; DWI, diffusion-weighted imaging; IVIM, intravoxel incoherent motion imaging; T2, T2 relaxation time mapping; T1, T1 relaxation time mapping; PD, proton density mapping; R2, R2* mapping.*

Up to this moment, only three studies performed daily measurements during treatment in humans (24, 79, 80). Mahmood et al. performed daily IVIM measurements in patients with brain metastases. They showed that the mean ADC increased for patients with responding brain metastases and decreased for non-responding metastases (79). From fraction seven onwards the distinction between responders and non-responders became more pronounced. The IVIM parameters, perfusion fraction f and pseudo-diffusion coefficient D*, did not show significant prognostic value. In another study, they showed that the size of the viable tumor delineated on DWI images and the ADC value of the viable tumor are a better predictor for outcome than the change in tumor size delineated on anatomical images (80). In a small, but unique, study with 8 rectal cancer patients, ADC values during treatment overlapped between complete and partial responders (24). Therefore, no significant differences in ADC dynamics were observed between the two groups.

The small number of studies with multiple measurements per patient may be explained by logistical challenges and the cost of MRI exams beyond standard-of-care. Here, the MRIgRT systems provide an opportunity. For patients who are treated on an MRIgRT system the logistical barrier is much lower as it only requires some prolonged time for imaging on the table (9). In fact, as the online adaptive workflow on MRIgRT systems takes up some time, quantitative imaging can be acquired during this time period, avoiding an increase in overall time on the table. As MRIgRT systems have been introduced in clinical practice recently (10), only a few qMRI studies have been performed so far. Feasibility of qMRI on MRIgRT systems was first demonstrated in a pilot DWI study. In this study, longitudinal DWI was acquired from a cohort of patients with head-and-neck cancer and sarcoma every 2-5 fractions throughout their treatment courses with different ADC change patterns observed (48). In a similar way, the feasibility of DWI for response assessment was shown in three rectal cancer patients (25). A pilot with four patients with brain tumors showed that changes in T1, R2* and proton density maps were detectable during the course of treatment (82). In addition, a few studies assessed the feasibility of using radiomic features to monitor response during treatment (96, 98, 99). For sarcoma patients it was shown that radiomic features derived from longitudinal DWI can be used to predict post-surgery tumor necrosis score after radiotherapy (98). The study of Boldrini et al. illustrated that changes in radiomic features during treatment have the potential to predict clinical complete response in rectal cancer (96). In addition, a pilot study showed that radiomic features could predict outcome for patients with pancreatic cancer treated with stereotactic ablative body radiotherapy on an MRIgRT system (99).

TECHNICAL VALIDATION

To integrate an MRI and a linear accelerator, modifications have been made to the MRI scanners in these systems. As a result, their technical specifications differ considerably from those of diagnostic systems. For the MRIdian (Viewray Technologies Inc. USA), the on-board MRI is a split bore superconducting magnet with a field strength of 0.35 T (109, 110). There is a 28 cm gap in between to reduce the number of MR components being in the radiation beam pathway. In case of the Unity system (Elekta AB, Sweden), the field strength is 1.5 T, but the gradient coils are physically split to create a radiation window (111). The 2 x 4 channel receive coil is radiolucent with all electronic components

at the edges of the coil (111). The reduced signal-to-noise ratio and gradient performance for both systems put constraints on the acquisition protocols and the performance of qMRI measurements. Therefore, first efforts have been taken to assess the performance of these measurements on MRIgRT systems with phantoms (48, 82, 112–114). For the MRIdian 0.35T MRI, a few DWI studies have been performed, demonstrating the ADC accuracy and reproducibility, as well as improving DWI spatial integrity (48, 112). Studies of Nejad-Davarini et al. (82) and Bydder et al. (113) also explored feasibility and accuracy of T1 mapping, R2* mapping, proton density mapping, and proton density fat fraction using MRIdian. A multicenter study showed that consistent ADC, T1, T2, and DCE values can be measured across institutes with a Unity system (114). The accuracy of the techniques was similar to previously reported literature on diagnostic scanners. In addition, the feasibility of these qMRI techniques was demonstrated for a prostate cancer patient. Phantom measurements showed that accurate ADC values can be obtained within a 7 cm radius of the iso-center (115). Outside this region, ADC values deviated more than 5%. To increase the time window during which qMRI data can be acquired, the effect of image acquisition during irradiation has also been investigated. Phantom images acquired during gantry rotation were negligibly different from images with a static gantry (116). However, bulk shifts in the order of one pixel were observed and the extent of the phantom was gantry angle dependent. Therefore, DWI with an echo planar imaging sequence may require special attention to geometrical shifts and distortions. With test-retest measurements in prostate cancer patients it was shown that the rotating gantry did not affect the repeatability of ADC measurements (115).

DISCUSSION

With BIGART two important concepts in radiotherapy are brought together. Recognizing the dynamic heterogeneity of a tumor during radiotherapy and adapting the treatment to the changing characteristics may widen the therapeutic window between tumor control and treatment-related toxicity. Although the two concepts have been around for over two decades, only now the technology is available to integrate daily biological imaging with online treatment adaptation. While many qMRI biomarker studies have been conducted, many more steps need to be taken before BIGART on MRIgRT systems becomes routine practice.

From a clinical perspective, the first step will be to investigate daily changes in qMRI values in different tumor sites. Multicenter observational trials should be initiated to validate these findings. In particular, it is important to investigate which qMRI techniques are suitable candidates for BIGART (117, 118). Based on the current and mostly consistent evidence, DWI seems to be a logical first choice to investigate further. The potential of DCE needs to be established, but might be very useful in certain applications (102). IVIM is an attractive alternative to study perfusion as it avoids administration of a contrast agent. Although previous studies observed a weak to moderate correlation between DCE and IVIM parameters (119–123), for BIGART it might be sufficient if similar trends are visible in the IVIM and DCE parameters. Other qMRI techniques are also promising, but must be investigated with larger populations. As different qMRI techniques reflect different aspects of tumor biology, a combination of techniques might give complimentary information with a higher predictive value for early treatment response (50, 53). Another open issue is the time scale at which changes in qMRI values happen during treatment. Some studies have reported changes early during treatment, others later. Monitoring changes on a daily basis, will help characterize this further. In addition, this will also reveal whether changes are homogeneous at group level (e.g. responder or non-responder groups), whether the time scale of the changes differs on patient-level or even differs within the tumor of the same patient. Furthermore, the relevance of observed changes in relation to treatment outcome (e.g. survival, recurrence, toxicity) needs to be established in order to identify if a biomarker potentially is predictive and suitable for BIGART.

Technical validation (124–126) of qMRI measurements on MRIgRT systems is required to ensure that the results are also relevant outside the MRIgRT domain, in particular because the MR-part of the MRIgRT systems is different from diagnostic systems. Digital and physical phantoms can be used to assess the accuracy and reproducibility of the qMRI measurements (127–134). Furthermore, to know which changes in qMRI values can be attributed to the effect of the treatment, assessment of the repeatability of the measurements should be performed with test-retest studies (125). Standardization of qMRI protocols could assist to improve reproducibility across participating centers (115).

In conclusion, MRIgRT systems have the potential to bring adaptive radiotherapy and biological targeting together in practice. The first step will be to investigate daily changes in qMRI values in different tumor sites, validated in a multicenter setting. Then, interventional studies become feasible to investigate the potential of qMRI as a biomarker for BIGART.

AUTHOR CONTRIBUTIONS

PH and UH contributed to the conception and design of the review paper. All authors contributed to the article and approved the submitted version.

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REVIEW
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MR-Guided Radiotherapy: The Perfect Partner for Immunotherapy?

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During the last years, preclinical and clinical studies have emerged supporting the rationale to integrate radiotherapy and immunotherapy. Radiotherapy may enhance the effects of immunotherapy by improving tumor antigen release, antigen presentation, and T-cell infiltration. Recently, magnetic resonance guided radiotherapy (MRgRT) has become clinically available. Compared to conventional radiotherapy techniques, MRgRT firstly allows for daily on-table treatment adaptation, which enables both dose escalation for increasing tumor response and superior sparing of radiosensitive organs-at-risk for reducing toxicity. The current review focuses on the potential of combining MR-guided adaptive radiotherapy with immunotherapy by providing an overview on the current status of MRgRT, latest developments in preclinical and clinical radio-immunotherapy, and the unique opportunities and challenges for MR-guided radio-immunotherapy. MRgRT might especially assist in answering open questions in radio-immunotherapy regarding optimal radiation dose, fractionation, timing of immunotherapy, appropriate irradiation volumes, and response prediction.

Keywords: magnetic resonance-guided radiotherapy, adaptive treatment, immunotherapy, radio-immunotherapy, preclinical

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INTRODUCTION

Over the last decades, substantial technical and methodological innovations in radiotherapy have enabled both more precise and focused delivery of higher doses of ionizing radiation combined with superior sparing of surrounding organs-at-risk (OARs). The latest development is magnetic resonance (MR)-guided radiotherapy (MRgRT), which bears the potential to revolutionize current standards and processes in radiotherapy. It not only offers superior soft-tissue contrast for precise detection of inter- and intrafractional changes in patient and tumor anatomy, but also allows for immediate reaction to these alterations by on-table plan adaptation (1–3). Thereby, safety margins can be reduced enabling dose escalation, while simultaneously limiting toxicity (4–7). Furthermore, some MR-linac devices offer gated dose delivery, which further facilitates irradiation of moving targets (8). Functional imaging, potentially integrated at the MR-linac, might allow for

biologically guided radiotherapy to identify treatment responders, who could benefit from dose de-escalation, while additional (subvolume) boost dose might foster tumor control in non-responders (9, 10).

Despite tremendous advances in radiotherapy for improving local control and minimizing side-effects during the last decades, distant progression outside the irradiation field still remains a major challenge. Recently, immunotherapy has emerged as the fourth pillar in cancer treatment besides surgical resection, systemic therapy, and radiotherapy. Immunotherapy is increasingly regarded as a promising and attractive partner to radiotherapy, as ionizing radiation is known to inherit potent immunomodulatory effects by enhancing tumor immunogenicity and fostering immune-mediated tumor regression not only locally but also distant to the irradiation field (11, 12). However, for optimizing efficacy and reducing toxicity of anticancer radio-immunotherapy, redefinition of conventional radiotherapy volumes, doses, and fractionation schedules might be necessary (13, 14). Biologically individualized, MR-guided adaptive radio-immunotherapy might offer unique features to approach these challenges.

CURRENT STATUS OF MR-GUIDED RADIOTHERAPY

Hybrid systems for MRgRT, combining MR-scanners with radiotherapy devices, have first been proposed at the beginning of this century, and were introduced into clinical practice within the last years (15–17). Currently, two different systems are commercially available. Both make use of on-board magnetic resonance imaging (MRI) for patient positioning and enable treatment with step-and-shoot intensity modulated radiation therapy (IMRT) (3, 18, 19). The systems also facilitate on-table treatment plan adaption based on the actual anatomic situation at the time of treatment. As the superior soft-tissue contrast of MRI allows for precise organ-at-risk delineation and therefore enables adaptive minimization of dose to normal tissue, it is expected that MRgRT will allow dose escalation (6).

With regard to targets susceptible to breathing motion, mid-position based treatments using four-dimensional MRI acquired in treatment position directly at the MR-linac have been described (20), as well as real-time beam gating controlled by two-dimensional cine-MR (8, 21). Both strategies can contribute to a reduction of margins and thereby also potentially enable dose escalation.

First clinical data has been reported for various indications, and multiple clinical studies are ongoing that aim to show the benefits of this technology. Among others, the treated indications include liver (22, 23), pancreas (22, 24), lung (5, 25–28), prostate (4, 29–31), breast (32, 33), head and neck (16, 34), and oligometastatic disease (7, 35, 36). Although MR-guided treatments in principle can be performed in standard fractionation schemes, several authors report on the use of MRgRT for hypofractionated/stereotactic treatment schedules (4, 34, 36–38) and even single fraction regimens (39, 40).

In addition, on-board MRI at MR-linacs can also be used for quantitative MRI, thereby potentially enabling treatment response monitoring as well as treatment plan adaption based on quantitative MRI information (9).

CURRENT STATUS OF PRECLINICAL RADIO-IMMUNOTHERAPY

Preclinical murine cancer models serve as an essential intermediate experimental model system to translate the findings from bench to bedside. In the radio-immunotherapy field, these models have extensively proven the high potential of combining radiotherapy with immunotherapy. Moreover, they have led to the identification of important underlying mechanisms. Preclinical evidence of synergy between radiotherapy and immune checkpoint blockade with anti-CTLA-4, anti-PD-1, or anti-PD-L1 has been obtained in numerous murine models of cancer (41–46). Many of the challenges of combining radiation with immunotherapy (e.g. radiotherapy dose and fractionation schedule as well as sequence of therapy) have been investigated and show that both immunogenic and non-immunogenic radiation dose and schedules exist (43, 47). It is now well-established that immunogenicity is related to sensing of cytoplasmic DNA by the cGAS/STING (cyclic-GMP-AMP synthase/stimulator of interferon genes) pathway (44, 47–49). Although these preclinical studies have provided essential new insights into the potential of radio-immunotherapy, they also have limitations. Most studies combining radiotherapy and immunotherapy only use a single ablative dose or a hypofractionated radiotherapy schedule and as a consequence the optimal timing, dose, and treatment regimen vary between models and are difficult to compare. To investigate the abscopal effect of therapy, the majority of the preclinical studies use a transplantable cell line that is injected subcutaneously in two distant locations in the mouse. In these models one tumor is irradiated and the abscopal effects are monitored in the untreated secondary tumor. In contrast to human metastatic cancer lesions, the genetic and environmental factors in the primary and secondary tumor are almost identical. These models thus may not fully recapitulate human metastatic cancer. Moreover, many small animal studies still use large field, single-beam irradiation. In these platforms, radiation exposure has limited accuracy and precision. Moreover, in-depth investigation into the anti-tumor response may be hampered by high dose radiation to healthy tissue. Data from murine experiments are important but should be carefully interpreted and used in the translation to a clinical situation. The need for more precise radiation and a growing appreciation for the role of the tumor microenvironment in anti-tumor (immune) responses has led to major developments in small animal imaging technologies (including SPECT, CT, MRI). Combining these technologies with small animal radiation research platforms enables to better mimic modern radiotherapy practice (50). Several efforts have already led to the development of small animal image-guided radiation

research platforms and showed their feasibility (51–56). Both for orthotopic (55) and genetically engineered mouse models of non-small lung cancer (51) preclinical image-guided radiotherapy platforms have been set up and demonstrated their feasibility to closely mimic clinical settings. Using a xenograft model of neuroblastoma, it was shown that small animal MRI-based radiotherapy planning not only allows for precision radiotherapy, but also for accurately measuring early tumor responses which are difficult to measure by calipers (54). Orthotopic mouse pancreatic tumors were treated with image-guided radiotherapy including treatment planning techniques comparable to patient treatment (52). Additionally, for spontaneous pancreatic tumors MRI guided radiotherapy platforms have been established (53).

To achieve the best predictive value of animal-based translational cancer research, models should provide biological mechanistic insights that can be tested in a clinical setting. This requires the availability of small animal image-guided radiotherapy platforms that evolve in line with advances in the clinic and suitable models in mice with a functional immune system that mimic human responses.

CURRENT STATUS OF CLINICAL RADIO-IMMUNOTHERAPY

In 1953, Mole et al. were the first to describe the so-called "abscopal effect" (from the Latin prefix *ab for* "away from" and *-scopus* for "mark or target") for the immune-mediated regression of unirradiated tumor lesions at distance from the primary site of local radiotherapy (57). However, prospective evidence for the clinical efficacy of radio-immunotherapy is still limited today (58).

Initial data is especially found in the treatment of oligometastatic cancer patients. Four phase II trials have previously demonstrated that the addition of metastasis-directed ablative therapy for all tumor sites to standard of care treatment significantly improved at least progression-free survival (PFS) or even overall survival (OS) in several different tumor entities (38, 59–62). Two recently published phase II trials included metastatic non-small cell lung cancer (NSCLC) patients treated with the anti-PD-1 antibody pembrolizumab with or without locally ablative therapies including SBRT (29, 63). The study by Theelen et al. aimed to assess whether SBRT on a single tumor site preceding pembrolizumab could enhance tumor response to immunotherapy and reported a doubled overall response for the experimental arm as compared to immunotherapy only. Although PFS was more than three times and OS more than two times higher in the SBRT arm, no significance was reached. The observation that the largest effect occurred in the PD-L1-negative subgroup suggests that radiotherapy may increase the responsiveness of non-inflamed NSCLC tumors to immune checkpoint inhibition (63). This needs further clinical evaluation. The second trial by Bauml et al. included 51 oligometastatic NSCLC patients who had received locally ablative therapy to all known sites of disease and were additionally treated with pembrolizumab. Median PFS for the locally ablative therapy arm was significantly superior with 19.1 months compared to historical controls with only 6.6 months ($p = 0.005$) (29).

As most current studies on MR-guided adaptive radiotherapy focus on the treatment of oligometastases, the combination of immunotherapy with MRgRT of oligometastases appears especially attractive. Henke et al. recently published results of a phase I trial of MRgRT including oligometastatic tumor lesions of different origin, while others concentrated on MRgRT of adrenal, hepatic, lymph node, or bone metastases (7, 17, 23, 35, 64, 65). Radio-immunotherapy with daily MR-guided plan adaptation bears the potential to further reduce toxicity and improve local control, while simultaneous immunotherapy might boost radiation-induced immune activation, block radiation-induced immunosuppressive effects, and eliminate microscopic disease (14).

Immunotherapy is expected to be most effective when treating patients with limited disease burden (66). Additional evidence for this hypothesis comes from the results of the PACIFIC trial, in which patients with unresectable stage III NSCLC who had responded to initial chemoradiotherapy, were treated with the anti-PD-1 antibody durvalumab (67). The addition of durvalumab nearly tripled the median PFS from 5.6 months to 17.2 months and significantly improved 2-year OS from 55.6 to 66.3% ($p = 0.005$). Furthermore, a *post-hoc* analysis of the KEYNOTE-001 trial demonstrated that previous radiotherapy in metastatic NSCLC patients receiving pembrolizumab significantly enhanced survival (6-months OS with radiotherapy 73% compared to 45% without) (68). Up to now, only few data are available regarding MR-guided adaptive radiotherapy for lung cancer patients (5, 25, 26). However, several studies have demonstrated a clear benefit of CT-guided adaptive radiotherapy for optimizing target coverage and sparing healthy lung tissue and hence toxicity (69–71). MR-guided adaptive radio-immunotherapy might therefore enable further dose escalation for improving local control, while simultaneously fostering the systemic immune response against distant micrometastases.

Current studies on MR-guided adaptive pulmonary radiotherapy focus on SBRT of small central and peripheral lung lesions (5, 25, 26). MR-guided adaptive SBRT of centrally or even ultracentrally located tumor lesions holds the promise to safely increase doses for such lesions adjacent to radiosensitive and vulnerable OARs (e.g. central airways, esophagus, heart). While local control following SBRT is usually satisfying, distant progression remains the major challenge (72, 73). Hence, several trials are ongoing to assess the efficacy of additional immunotherapy with SBRT for eradicating microscopic disease and fostering RT-induced immune activation in the treatment of early-stage lung cancer patients (e.g. KEYNOTE-867, PACIFIC-4). MR-guided adaptive radio-immunotherapy would further allow for safe treatment of critically located pulmonary lesions with sufficiently high dose and simultaneously reduce the occurrence of new distant tumor lesions.

As discussed above, systemic responses to immunotherapy are more frequent if overall disease burden is limited. In line with

this concept, Golden et al. analyzed the occurrence of abscopal responses in metastatic patients on chemotherapy treated with concurrent radiotherapy (35 Gy in 10 fractions) to one metastatic site and granulocyte-macrophage colony-stimulating factor (12). Interestingly, the authors described that abscopal tumor responses were more frequent in patients with limited disease sites (73% in patients with only three metastases). Further support for this assertion comes from another trial, in which patients with metastatic castration-resistant prostate cancer were treated with a single dose of 8 Gy to a single bone metastasis with or without ipilimumab (74). Patients with only one osseous metastasis were more likely to benefit from immunotherapy compared to those with more bone lesions. In these scenarios, MR-guided adaptive radiotherapy could enable highly precise and focused dose delivery even to critically located tumor lesions, for which conventional techniques cannot achieve sufficiently high doses, while simultaneously potentiating local effects of immunotherapy (14).

Further tumor entities like head-and-neck tumors, rectal, cervical, or bladder cancer are expected to profit from MR-guided adaptive radiotherapy for not only enabling dose escalation, sparing of adjacent radiosensitive OARs but also for increasing the chance for organ preservation (1, 75–78). Up to now, immunotherapy is only clinically established in the treatment of metastatic tumor stages of these malignancies (79–83). Future studies are awaited to demonstrate the benefit of simultaneous radio-immunotherapy to augment local and systemic immunity and potentially reduce the risk for metastatic recurrences.

MR-GUIDED RADIO-IMMUNOTHERAPY: CHALLENGES AND OPPORTUNITIES

Preclinical models suggest a window of opportunity to combine radiotherapy and immunotherapy, and early clinical studies report favorable responses to this combination. Nevertheless, many parameters remain ill-defined and need to be resolved to fully exploit the potential of radio-immunotherapy (84). These include scheduling of both modalities, fractionation regimens, treatment volume, and response prediction. The MR-linac combines unique functionalities that can address some of these outstanding questions. With regard to the optimal sequence of both modalities, preclinical data are not conclusive and suggest a combined effect that is both tumor model and immunomodulatory agent dependent. Although results from clinical studies are still scarce, the data indicate highest (local and abscopal) efficacy when radiation shortly precedes or is given during immunotherapy (67, 68, 85). Whether or not early radiation-induced influx of immune cells in the tumor microenvironment can be detected by MR imaging, e.g. as increased ADC values on DW MRI (86), and guide the optimal timing of immunotherapy, remains to be investigated.

Preclinical models imply that the dose per fraction is critical for the immunogenic effect of radiation and that a moderately hypofractionated regimen (range: 8–12 Gy per fraction) induces sufficient cytosolic double-stranded (ds)DNA to stimulate the cGAS-STING-Interferon type I pathway. Too high radiation doses (>12–18 Gy), however, can lead to the activation of feedback mechanisms, like the induction of the exonuclease Trex1 that degrades cytosolic DNA and attenuates the cGAS-STING pathway (47). This delicate biological balance between release of dsDNA and Trex1 dictates dsDNA accumulation in the cytoplasm of irradiated cells, and the subsequent initiation of anti-tumor immune responses. The dose range at which such optimal conditions arise, may turn out to be tumor specific, although in general a relatively high dose per fraction (around 8 Gy) seems required. MR-guidance is an obvious tool to safely and accurately deliver these high doses of radiation and allow the identification of the most effective fractionation regimen for synergy between radiotherapy and immunotherapy.

With respect to the ideal target volume to be irradiated, MR-based functional imaging could reveal radiosensitive or radioresistant subvolumes of tumors that may benefit from differential dosing. Intriguingly, partial tumor irradiation has been shown to elicit an effective (both local and abscopal) immune response without the need to treat the entire tumor (87, 88). High precision delivery of radiation in the context of radio-immunotherapy also involves sparing of lymphoid tissue. In fact, avoiding irradiation of tumor-associated draining lymph nodes may be crucial for the integrity of the immune response. In the context of a preclinical model comparing stereotactic radiotherapy with or without elective nodal irradiation in combination with immune checkpoint blockade, it was found that an altered T-cell chemoattractant chemokine signaling resulted in reduced immune infiltration as well as in an unfavorable balance between tumoricidal and immunosuppressive immune cells (89).

A final challenge pertains to the need for robust biomarkers of response. The superior soft tissue contrast of MR increases the ability to define the location of the tumor and adjacent normal tissues and to adapt treatment based on biological and functional dynamics of both tumors and normal structures that may occur during treatment. As responses to radio-immunotherapy will vary among tumor sites, pathological subtypes and individual patients, there is a strong clinical need for solid predictors of response to treatment. In addition to tissue-based biomarkers [such as T-cell–inflamed gene-expression profile, programmed death ligand 1 (PD-L1) expression, and tumor mutational burden], imaging-based biomarkers are emerging as promising, non-invasive, and repeatable tools that may help identify patients who have a higher likelihood of response to radio-immunotherapy across a broad spectrum of tumors. The MR-linac not only allows the use of functional MR sequences, quantitative feature extraction using radiomic approaches has become available to develop such imaging-based biomarkers, including for radio-immunotherapy. Recently, a CT-based radiomic signature was developed and validated to assess tumor-infiltrating immune cells and response to immunotherapy in patients with advanced solid tumors (90). A comparable approach using MR-based information is an obvious opportunity and will be discussed in more detail in a separate contribution to this special issue.

CONCLUSIONS AND FUTURE PERSPECTIVES

The clinical implementation of MR-guided adaptive radiotherapy has led to new approaches to compensate for poor target definition. Superior soft tissue contrast combined with real-time plan adaptation now allows to reduce margins, increase the dose per fraction and integrate functional information in highly individualized treatment plans. These features make MR-guided radiotherapy the perfect partner for immunotherapy. Radio-immunotherapy has emerged as a promising combination for the treatment of local and abscopal disease, but the conditions for synergy need further optimization. MR-guided radiotherapy could be instrumental to address some of these variables, including optimal doses and fractionation schedules, timing of both modalities, reduced delivery volumes (partial tumor irradiation; sparing draining lymph nodes), and response prediction. This requires a collaborative effort, standardization of protocols, models, and methodologies, and a systematic collection of imaging and biomaterial data.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of this review. JH-R, SK, MA, and MV drafted the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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MR-Guided Adaptive Radiotherapy for Bladder Cancer

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Radiotherapy has an important role in the curative and palliative treatment settings for bladder cancer. As a target for radiotherapy the bladder presents a number of technical challenges. These include poor tumor visualization and the variability in bladder size and position both between and during treatment delivery. Evidence favors the use of magnetic resonance imaging (MRI) as an important means of tumor visualization and local staging. The availability of hybrid systems incorporating both MRI scanning capabilities with the linear accelerator (MR-Linac) offers opportunity for in-room and real-time MRI scanning with ability of plan adaption at each fraction while the patient is on the treatment couch. This has a number of potential advantages for bladder cancer patients. In this article, we examine the technical challenges of bladder radiotherapy and explore how magnetic resonance (MR) guided radiotherapy (MRgRT) could be leveraged with the aim of improving bladder cancer patient outcomes. However, before routine clinical implementation robust evidence base to establish whether MRgRT translates into improved patient outcomes should be ascertained.

Keywords: adaptive radiotherapy, bladder cancer, MR guided radiotherapy, MR-linac, MRI

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INTRODUCTION

Bladder cancer is the ninth most common cancer diagnosis globally with over 390,000 new cases and over 150,000 deaths occurring each year (1). Muscle invasive bladder cancer (MIBC) makes up approximately 20% of patients at presentation. For these patients, cure is achieved through both effective local treatment and systemic treatment (2, 3).

Radical cystectomy has been the internationally accepted main stay of local treatment for MIBC (4). This requires removal of the bladder, which then necessitates a urinary diversion. Most commonly, this is in the form of an incontinent stoma (ileal conduit). Continent stomas and orthoptic neo-bladder reconstructions are feasible options for some patients. Despite this, continence and sexual function impact significantly on quality of life post-operatively (5–8). A highly selected proportion of patients may be suitable for partial cystectomy by virtue of having a unifocal tumor in a region of the bladder which then permits an adequately safe margin to be

obtained without compromise to the bladder capacity. As less than 5% of patients meet these stringent criteria, removal of the whole bladder will be necessary for almost all patients. The clear absence of comparable functional organ substitutes following surgery means that bladder preservation with radiotherapy offers opportunity for cancer cure with organ preservation (3, 9, 10).

Concerns about oncologic equivalence and absence of randomised control data have driven underutilization of radical radiotherapy for the treatment of MIBC (11–13). However, when radiotherapy is used as part of a multi-modality strategy, it achieves similar survival outcomes to radical cystectomy (14, 15). The 5-year cancer-specific survival ranges from 50% to 82% (depending on initial stage), with 5-year overall survival of approximately 50%. Long-term bladder preservation is successfully achieved in up to two-thirds of patients (9). As a result, it would be accepted that patients should be offered opportunity to consider both modalities when either radical treatment would be suitable (3, 10, 16).

The aetiological association of bladder cancer with smoking means patients often have multiple comorbidities on a background of increasing frailty with advancing age that may restrict opportunity for either radical treatment options (17). For these patients, hypofractionated radiotherapy offers prospect for long-term disease and symptom control (18, 19).

In both the radical and palliative bladder radiotherapy settings, there remains opportunity to improve clinical outcomes further by overcoming some of the challenges that bladder radiotherapy poses. In this article, we examine the technical challenges of bladder radiotherapy and explore how magnetic resonance (MR) guided radiotherapy (MRgRT) could provide a solution for geometric and biologically adapted treatment delivery.

CURRENT ROLE OF MR IMAGING IN BLADDER CANCER

The tumor staging of bladder cancer is contingent on accurately determining the presence of muscle invasion. Given the different treatment approaches for NMIBC and MIBC, establishing the correct tumor stage is critical in deciding the correct treatment strategy (3, 20). Although CT provides high spatial resolution allowing visualization of extra-vesical spread, it is not a reliable means of determining the extent of muscle involvement (21). It is limited both by inter-observer variability and inability to distinguish the muscle layers of the bladder (22, 23). As a result, the current standard means of diagnosing and staging MIBC remains performing a TURBT with the aim of ensuring bladder muscle is included in the specimen so that its involvement can be ascertained (3, 20, 24). However, TURBT remains imperfect as it risks under staging in 25%–50% of patients (25–27).

Magnetic resonance imaging (MRI) staging accuracy exceeds those reported for TURBT in terms of distinguishing between MIBC (≥T2) and NMIBC (≤T1) (28, 29). Three meta-analyses have evaluated the performance characteristics of multi-parametric MRI (mpMRI) for local tumor staging across approximately 5,000 patients. These studies reported similar results, with pooled sensitivity of 0.87 (95% Confidence interval, CI 0.82–0.91), 0.90 (95% CI 0.83–0.94), and 0.92 (95% CI 0.88–0.95), and specificity of 0.79 (95% CI 0.72–0.85), 0.87 (95% CI 0.78–0.93), and 0.88 (95% CI 0.77–0.94) (28–30).

A mpMRI examination for bladder cancer staging usually consists of a T2-weighted image (T2W) with diffusion-weighted image (DWI), or dynamic contrast enhancement (DCE) image (28–31). There is suggestion however that mpMRI using DWI is the optimal protocol for tumor staging of bladder cancer (29, 30). **Figure 1** illustrates example image of a localized MIBC as evaluated on 1.5T MRI.

In order to standardize the image acquisition, interpretation, and reporting of mpMRI for newly diagnosed bladder cancer, the Vesical Imaging-Reporting and Data System (VI-RADS) was developed in 2018 (31). This is a five-point qualitative scoring system of bladder tumors as seen on T2W, DWI, and DCE imaging, to determine the likelihood of muscle invasion. The final score is based on T2W imaging because of its high spatial resolution to evaluate the integrity of the muscle layer. Definitive muscular invasion is decided by the assessment of DWI and DCE. However, as DWI improves the accuracy of distinguishing MIBC, it is relied upon particularly when there is discordant scoring between T2W and DCE sequences (29, 31–33).

Multi-institutional studies applying VI-RADs scoring (1-5) to mpMRI interpretation to determine local staging demonstrates high sensitivity and specificity when a cut off score of ≥3 is used to describe likelihood muscle invasion (34–38). VI-RADS scoring also reflects good to excellent interobserver reporting agreement, with indices of agreement ranging between 0.73 and 0.92 (34–37). Despite this evidence, mpMRI has not yet established its place as recommended and preferred standard imaging for local bladder cancer staging in clinical guidance (3).

In prostate cancer mpMRI has been shown to identify those men who could safely avoid unnecessary biopsy with the aim of enabling detection of clinically significant disease (39). In bladder cancer, it is also hypothesized that mpMRI may also serve as a triage test prior to TURBT (40). The advantage this presents for MIBC patients is that it would potentially reduce delays to definitive treatment, avoids under staging on initial TURBT, and minimizes the risk of systemic circulating cancer cell dissemination occurring as a result of bladder perforation with TURBT (25, 26, 41, 42). The possibility that the TURBT may be completely avoided when suspicion of MIBC is high on mpMRI is being explored in a randomized phase 2/3 trial (BladderPath, ISRCTN reference number 35296862) (43). This trial aims to compare the standard diagnostic pathway consisting of flexible cystoscopy and biopsy, with imaging followed by TURBT versus a risk stratified imaging directed pathway whereby if on flexible cystoscopy there is clinical suspicion of possible MIBC, a biopsy is taken and patients proceed to mpMRI. If the mpMRI supports likelihood of NMIBC, patients then proceed to TURBT otherwise if the mpMRI supports likelihood of MIBC patients proceed to directly to treatment. Initial feasibility to randomize possible MIBC patients to a TURBT directed diagnostic pathway or mpMRI directed

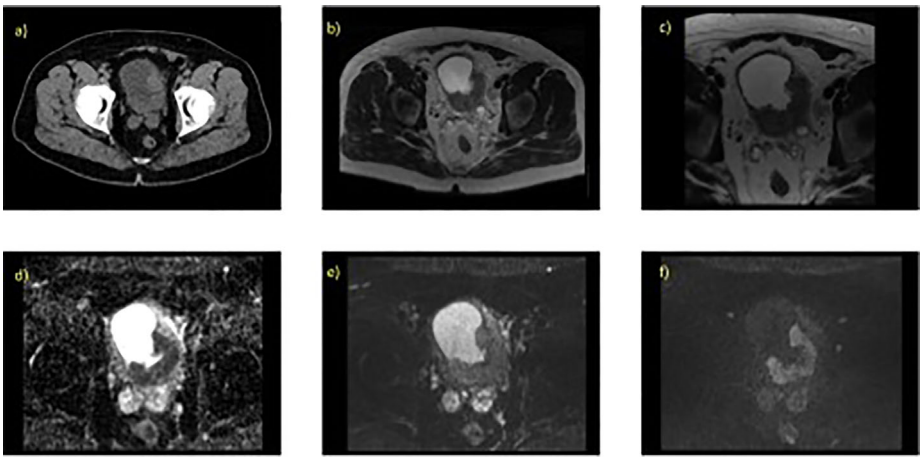

FIGURE 1 | Localized MIBC as evaluated on T2W and DWI with the associated parameter settings for 1.5T MRI. 70 year old male with known T3 N0 M0 bladder cancer, tumour is present at the left ureteric orifice (extending posteriorlaterally) **(A)** contrast enhanced CT scan, axial slice through pelvis, **(B)** axial T2W (large field of view) showing hypo intense lesion, **(C)** axial T2W small field of view **(D)** corresponding ADC map, **(E)** axial DWI at b-value 0, **(F)** axial DWI at b-value 750.

diagnostic pathway has been successfully demonstrated. The trial is ongoing to investigate how a mpMRI-driven diagnostic pathway impacts on time to correct therapy for MIBC and NMIBC and clinical progression-free survival (43).

RATIONALE FOR MR-GUIDED ONLINE ADAPTIVE BLADDER RADIOTHERAPY

MRI Improves Target Visualization

The uncertainties of using CT for bladder tumor staging also impact on the ability to reliably define the outer bladder wall and gross tumor volume (GTV) within the bladder. As a result, use of CT leads to significant inter-observer target delineation variability particularly at interfaces with neighboring structures such as small bowel or prostate, and in the presence of extra-vesical spread (44–47). Poor target delineation is a major source of systematic inaccuracies in radiotherapy (45). The improved soft tissue contrast of MRI may help address this.

The GTV visibility in bladder cancer however can be hampered after TURBT and good response to neo-adjuvant chemotherapy (46). Insertion of radio-opaque markers at cystoscopy to demarcate the visible tumor extension has been explored (48). Surgical clips or gold fiducial markers can be inserted at the borders of visible tumor or tumor bed *via* cystoscope (49–51). Although they provide excellent visualization on CT, these markers are prone to migration and fall out in up to 50% of cases following implantation (49, 52). Diathermy post insertion or gold seeds with micro-tines further improve retention rates but net marker losses (up to 18%) are still seen (50, 51). Metallic fiducial markers do not yield a signal on MRI and appear dark. By using T2*weighted sequences, the signal loss can be emphasized such that their position can be identified allowing them to be used to guide localization on MRI (53).

Iodized oil contrast (Lipiodol®), 0.25–0.50cc injected sub-epithelially into the bladder wall has also been used as an alternative fiducial marker (54–57). Its use is limited to patients with no history of contrast medium sensitivity or active thyroid disease (54, 58). It is not subject to the same frequency of marker loss, but the liquid nature of the contrast medium means intra- and extra-vesical spillage can occur (54–56). In circumstances of high concentration, this can lead to streak artefacts on CT (59, 60). Lipiodol is not visible on MRI.

Novel radiographic gel-like markers (BioXmark®) that are liquid, with low initial viscosity prior to and during injection but transforms into a highly viscous liquid to form a 3D gel-like shape have also been investigated (61). It produces signals void on MRI in phantom studies (62). Further work is in progress to assess this marker when used clinically for bladder MRI evaluation.

Adaptive Radiotherapy to Address Target Motion

The bladder is relatively mobile target subject to filling variation and deformation. It is fixed at the caudal pole and is abutted by the rectum or uterus posteriorly. Therefore, as the bladder volume increases non-uniform organ expansion generally occurs which is more pronounced in the cranial and anterior directions (47, 63–66). The magnitude of this change is rarely consistent or predictable (67, 68). Patient interventions such as drinking protocols, catheterization, dietary modifications, and laxatives have been explored but do not consistently reduce bladder target variation (60, 69, 70).

Inter-Fractional Motion Mitigation

In an attempt to compensate for both the variability of the bladder shape, and size between treatments (inter-fraction), historically large population-based margins (up to 1.5–2cm) have been applied to create the planning target volume (PTV).

Despite the use of such large margins to address the bladder target positional uncertainties, without the adoption of soft tissue image guidance, geographical misses will occur at treatment delivery (71).

Pre-treatment, in-room three-dimensional volumetric soft tissue imaging provides anatomical information that can feedback into the plan and adapt dose delivery optimization (72). The overall aim of these adaptive radiotherapy strategies is to further improve the fidelity of dose delivered to target in order to reliably reduce the PTV so dose to normal tissues can also be reduced. In bladder cancer radiotherapy, two main adaptive approaches based on the wide availably of cone bean CT (CBCT) have seen drift into clinical practice based on reported dosimetric gains (68, 73).

The composite volume method is an offline adaptive radiotherapy approach that utilizes information from the verification CBCT acquired for the first 3–5 fractions to determine a patient specific internal target volume (ITV) informed by the maximal excursions of the bladder actually occurring. A smaller margin to account for remaining residual uncertainties is then applied to create a new PTV and plan. This solution adequately maintains bladder target coverage and reduces the PTV by approximately 40%–50% compared to population based PTV approach (74, 75). The main disadvantage is that patients can only benefit from the adaptive radiotherapy strategy after sufficient number of verification CBCTS images has been acquired. This presents limitations in its application to hypofractionated regimes because a significant proportion of treatment course would already have been delivered before a new plan can be created.

The alternative and more widely adopted method currently employed is to generate a library of patient specific treatment plans with varying PTV sizes (73). Using the CBCT acquired prior to each fraction, the anatomy is assessed to select the most appropriate plan that covers the bladder target with minimal normal tissue exposure. The library of plans can be created by applying either variable margins or by modeling the patient's own bladder filling pattern using either serial planning CT scans or the verification CBCTs from the initial fractions (76–78). This solution also successfully maintains target coverage, and reduces the PTV by approximately 40% with subsequent reduction in normal tissue irradiation (79). The main disadvantage is that a discrete library created to cover the spectrum of interfraction variation means the individual conformity of the selected plan to the imaged bladder on the day can be relatively poor (80). It is also possible in some circumstances that none of the plans in the library encompass the imaged bladder target on the day (78, 80).

Modeled approaches in bladder cancer radiotherapy illustrate that by adopting an online replanning adaptive radiotherapy process, whereby the patient's treatment plan is produced based on the actual anatomy seen while they are on the treatment couch would further improve target coverage and OAR sparing (81, 82). In work comparing standard single plan, with different adaptive strategies the volume of normal tissue receiving more than 95% of the prescribed dose was reduced to 66% (range 48%–100%) with library approach and to 41% (range 33%–50%) with daily re-optimization (81). Considerable normal tissue sparing potential therefore exists for bladder cancer patients with online re-optimization.

The availability of hybrid systems that incorporate both MRI scanning capabilities and linear accelerator (MR-Linac) allows an in-room, real-time MRI scan to be obtained immediately prior each fraction (83–85). As MRI yields superior soft-tissue contrast compared to CBCT it would be preferred means for accurate bladder target delineation and organs at risk (OARs), i.e., rectum and bowel identification to inform re-optimization at each fraction (86). Feasibility of these platforms to deliver an MR-informed fully online re-optimized new bladder plan at each fraction has been demonstrated (87, 88).

Intra-Fractional Motion Mitigation

Stochastic variation in the organ filling, deformation, and peristaltic motion means that changes will occur in the bladder target and OARs within the time scale of pre-treatment imaging and delivery of each individual treatment fraction. This necessitates additional consideration to determine the best means of accommodating for this motion in order to minimize risk of geographical miss.

The most common strategy in bladder cancer radiotherapy is to treat on an empty bladder and passively manage intra-fractional change by the application of a margin that will encompass the magnitude of motion likely to occur within the time frame of the workflow. For treatment delivery based on the CBCT adaptive solutions described above, intra-fraction margins ranging from 2 mm to 7 mm have been suggested (76, 77, 79, 81, 89, 90). This margin may also be influenced by treatment technique, as intensity modulated arc therapy (IMAT) is associated with faster delivery times than fixed field IMRT so facilitating use of smaller intra-fraction margins (91).

In a patient population who had serial MRI scans acquired at 2 minute intervals for up to 10-min post voiding, it was possible to demonstrate that the application of anisotropic margins (14 mm cranially and anteriorly, 9 mm posteriorly, and 5 mm in all other directions) successfully maintained target coverage as evaluated on the 10-min MRI scan for the entire treatment course (82). Target under dosing (≥D1cc <95% of the prescribed dose) was seen in 4% of fractions compared to 20% when a 5 mm isotropic margin was used (82).

Currently, treatment workflow times for utilization of an MRgRT online reoptimization approach are in the region of approximately 30–40 min (87, 92, 93). It has been successfully shown that an anisotropic margin of 15 mm applied cranially and anteriorly, 1 cm posteriorly, and 5 mm in all other directions will successfully maintain target coverage in 96.6% of fractions as assessed on the post treatment MRI scan (87). The mean conformity of the 95% isodose to the post treatment bladder target is 2.4 (range 1.5–3.6), suggesting the intra-fraction margin could be reliably reduced in some instances (87). While maintenance of target coverage throughout the fraction delivery is a priority, the potential gains of online re-optimization would be mitigated by the use of over-generous intra-fraction margins.

The alternative approach is to actively manage intra-fraction change with MR guided motion management. During beam on period, continuous MR imaging can be acquired for real-time motion monitoring, tracking, and or gating. A tracking slice is positioned to include a cross-sectional axis at the target volume of interest. A minimum tracking boundary or motion monitoring structure is set such that if a pre-specified proportion of the tracked target leaves this boundary, the beam will turn off (10). This allows extremes of anatomical changes to be detected while the target is being irradiated to minimize the risk of a geographical miss (10, 94).

MR guided tumor tracking has been successfully used on the MR-Linac for treatment of tumors of the upper abdomen and prostate (95–97). However, the challenge this presents for bladder cancer radiotherapy is that tracking alone is not necessarily a universal solution if the target is increasing in overall volume as occurs with whole bladder radiotherapy (65, 66). It raises the question then, could the tumor itself be tracked and could this region be safely prioritized over the uninvolved bladder.

Enabling Tumor-Focused Partial Bladder Irradiation

Tumor-focused partial bladder radiotherapy is attractive for two main clinical reasons: firstly, the reduced high dose opens the possibility that treatment-related toxicity could be reduced; and secondly, it opens the possibility for dose escalation to the tumor beyond limits currently determined by the whole bladder tolerance of 64-65Gy in 2Gy per fraction (98–100).

Whole bladder radiotherapy has been the accepted convention even in the presence of unifocal disease possibly because of the difficulty in identifying the tumor within the bladder on CT and the historical inaccuracies of treatment delivery described above. Nevertheless, evidence to date supports that partial bladder irradiation is likely to be safe (3, 101–103).

Bladder brachytherapy has been used for a highly select patient population with unifocal small lesions (≤50 mm) achieving similar outcomes to a matched population undergoing radical cystectomy (104). It is not widely accepted or recommended as an organ-conserving treatment option mainly because technical expertise is confined to highly specialized centers and no randomized control data is available (3, 101).

Randomized control trials of whole bladder versus tumor-focused partial bladder external beam radiotherapy have successfully demonstrated that tumor-focused partial bladder radiotherapy could be utilized with no adverse effect on local control (103, 105). However, these randomized controlled trials failed to show decrease treatment related toxicity (103, 105). A number of technical aspects are likely to have mitigated any benefit from a reduced high dose volume. Treatment was planned and delivered on an empty bladder. In addition, delineation of the tumor within the bladder using a planning CT scan would have invariably led to overestimating the GTV size (44–46). The subsequent isotropic 1.5 cm expansion margin around the GTV to generate the PTV boost volume from which a 3D conformal treatment plan was created would then leave very little additional normal tissue sparing compared to whole bladder treatment. Setup in the era of these trials was either to skin or bone and preceded soft tissue verification, so it can be assumed that with 1.5 cm margin target coverage may have only been approximately 60% (71). Dose unsuccessfully delivered to target would have resulted in unwanted normal tissue irradiation.

Many investigators have sought to overcome these challenges by using library of plans to deliver tumor-focused high dose radiotherapy on filled or partially filled bladder (80, 106, 107). The advantage of striving for a fuller bladder in these circumstances is that it reduces dose to the uninvolved bladder and provides greater opportunity for normal bladder sparing. Treatment delivered in these trials used either fixed field IMRT or IMAT. This improves conformity of radiation fields around the target volume, relative to 3D conformal techniques (91). In comparisons of clinical outcomes of bladder cancer radiotherapy, IMRT has been reported to significantly reduce acute CTCAE grade ≥2 diarrhoea compared to 3D conformal radiotherapy (56% versus 30%; $p = 0.008$) (108). Whether using library of plans to escalate tumor-focused dose translates into clinically meaningful outcomes will be evaluated in an international randomised phase II trial (RAIDER, NCT02447549) (109).

Dosimetric analysis of library of plans to deliver tumor-focused high dose radiotherapy reveals that although excellent target coverage can be achieved meeting normal bladder and bowel constraints, the high mean conformity of the 95% isodose of the selected plan to the tumor boost as seen on CBCT is 5.0 (SD 2.2, range 2.1–21.4) and the whole bladder is 3.5 (SD 1.0, range 1.7–8.9). This suggests large volume non-target irradiation is still occurring (80). The MR-Linac may therefore open opportunity for an online re-optimized tumor-focused partial bladder approach.

Successful tumor-focused partial bladder irradiation is dependent on ability to define GTV on both the planning CT and CBCT. Although CBCT allows reasonable discrimination of the bladder wall, visualization of the tumor itself is challenging (80, 110). As local recurrences occur most frequently at the original MIBC tumor site, correctly identifying the GTV becomes increasing critical particularly in the era of margin reduction (111). The superior soft tissue contrast of MRI may therefore enable more reliable tumor-focused partial bladder radiotherapy (**Figure 2**).

The MR-Linac may also provide greater opportunity to assess how the tumor moves in relation to the filling status of the bladder to determine the most appropriate intra-fraction margins for partial bladder radiotherapy. Work to date suggests that the bladder tumor is relatively rigid and non-elastic compared to non-tumor-bearing bladder regions but this is based on CT interpretation (112).

WORKFLOW CONSIDERATIONS FOR BLADDER TREATMENT ON THE MR-LINAC

An overview of the principal workflow components is presented in **Figure 3**. For treatment of the whole bladder on the

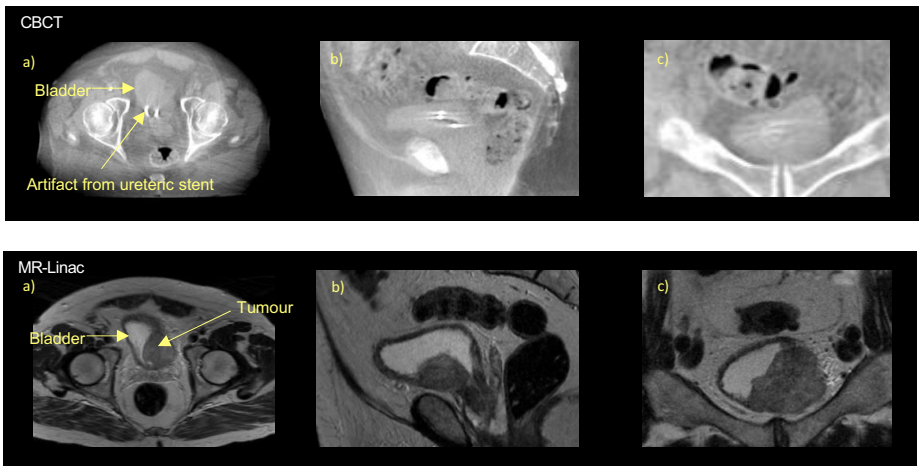

FIGURE 2 | Online pre-treatment CBCT and MR (T2W) images. Bladder tumour at left bladder wall as seen on axial a), sagittal b), and coronal c) views of the pelvis on corresponding CBCT and T2W taken on the MR-Linac, here urine appears bright and tumour dark/hypointense.

MR-Linac, workflow time pressures are critical because of the anticipated intra-fraction volume increase. If workflow time could be reduced, the margins currently applied to accommodate for this change could also be reduced. Several considerations can assist with achieving this.

Ideally as little time as possible should be spent re-optimizing the daily treatment plan. This can be aided by generating a robust planning class solution from the outset to minimize the need for online modification and experimentation. This should be robust to the expected daily changes in anatomy that will occur.

Prior to starting treatment, a reference plan is created. A planning CT ($CT_{planning}$) and, or a simulation MR ($MR_{planning}$) scan is acquired with an empty bladder. This is achieved by asking the patient to void immediately prior to scanning. The $CT_{planning}$ is used for density information and it is deformably registered to the $MR_{planning}$. It is also possible that at simulation serial images over time are acquired to estimate a "patient specific" intra-fraction bladder filling PTV margin.

When patients attend for treatment, they are asked to void their bladder immediately prior to set up. A session or pre-treatment MRI ($MR_{session}$) image is acquired on the MR-Linac which is registered to the planning reference image ($CT_{planning}$ or $MR_{planning}$). The contours from the planning reference image are propagated to the $MR_{session}$ image using deformable registration or segmented using artificial intelligence contouring algorithms (113). The contours are reviewed and corrected if necessary. To speed up the outlining time, more accurate delineation of OARs is limited to a 2 cm region around the target. The consequence of

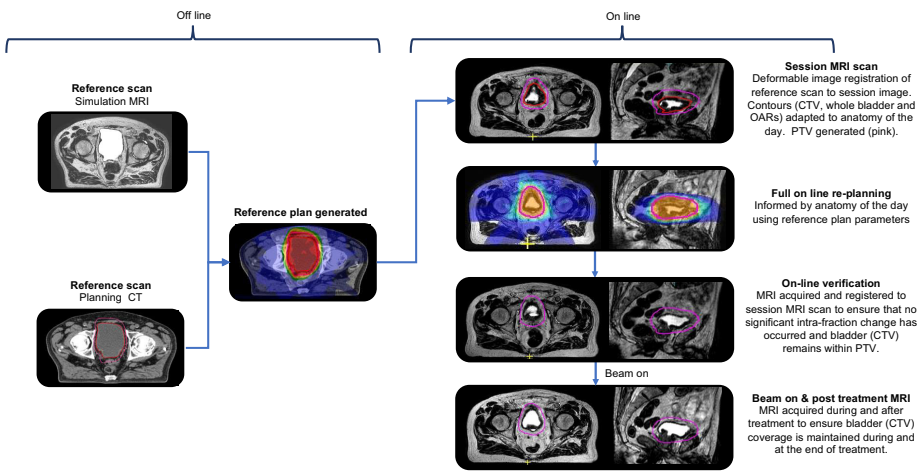

FIGURE 3 | Overview of the principal workflow components of online reoptimization using MRgRT.

having less accurate contours is that, although the dose distribution will still be close to optimal, the reported dose statistics for these OARs will be less reflective of actual dose to these structures. This trade-off is made to balance the desire for accurate delineation and the fact that the OARs underlying those contours are continuously changing whilst they are being delineated.

A new plan with full re-optimization is created. For online bladder planning dose-volume metrics do not have to be used, instead focus can be placed on how rapidly the dose falls off away from the target. Here, the optimizer only considers the dose gradient in the region where the OAR abuts the target, and as such is not dependent on the overall OAR volume. This approach is also less sensitive to accurate delineation of the OARs, as only the approximate region where they border the target is needed.

During the optimization process, a fast T2W MRI ($MR_{verfication}$) is acquired to confirm that appropriate target coverage is maintained either by reviewing the PTV coverage of the bladder or the isodose coverage of the bladder. If the bladder is not optimally covered then the plan can be shifted relative to the isocenter and dose recalculated on the $MR_{session}$ (114, 115). If this maneuver would also not sufficiently cover the bladder target then it would be recommended that the patient is removed from the couch, voids their bladder, and are treated with the reference plan. Prior to the subsequent fraction patient factors contributing to rapid bladder filling, i.e., pre-treatment diuretic or excessive hydration should be explored and managed. It may also be necessary to review and increase the intra-fraction margin.

At treatment delivery, cine MR can be used to monitor bladder motion during beam on with the option that should the bladder move out of the PTV or the pre-defined motion monitoring structure, the treatment can be interrupted if required. A post treatment T2W MRI (MR_{post}) is acquired immediately following delivery for offline dose assessment of the treatment delivered. The difference between planned dose on $MR_{session}$ and delivered dose as determined on MR_{post} could potentially be incorporated into the online adaption strategy and compensated for at the subsequent fractions, if clinically indicated.

Currently the time to deliver this workflow at best is between 15 and 27 min (personal communication, A Bertelsen & C Nyborg, Odense University Hospital, Denmark) but we have found the median total time for patients on the treatment couch is 39 min (range 33–48) (87). We expect that this will be reduced further with faster image acquisition, improvements in auto-contouring, increased computational ability for plan optimization and dose calculation, and the implementation of IMAT delivery techniques.

BEYOND GEOMETRIC ADAPTION

MRI could be used to acquire biological information about the bladder tumor. This could provide opportunity to develop MRI informed biologically adapted radiotherapy approaches (116).

DWI is a functional imaging technique dependent on the inhibitory effect of cell membranes to the random motion of water molecules. The higher cellular density of tumors compared to normal tissue means they demonstrate higher signal intensity, i.e., restricted diffusion on MRI, reflected quantitatively in a low mean apparent diffusion coefficient value (ADC). Per pixel ADC throughout the tumor volume can be used to capture the regional heterogeneity known to exist within tumors which may have prognostic and predictive value (117–121). As the local relapse site following radiotherapy is at the site of the MIBC tumor, it is hypothesized that by escalating dose to the tumor region of highest cellularity, local control rates could be improved (111).

Following successful treatment, the ADC value increases, reflecting decrease in cellularity. In MIBC ADC change is an independent predictor of pathological response (122, 123). Given serial DWI acquisition on the MR-Linac is possible at each fraction, there is potential for monitoring ADC change throughout treatment with identification of early non-responders who may benefit from change in treatment approach (124). As such MRI offers opportunity for a response adapted radiotherapy delivery.

Tumor hypoxia in MIBC is a potential predictor of radiotherapy response with effective modification improving outcome (125, 126). MRI can be used to measure and map tumor hypoxia in a number of ways not otherwise possible on biopsy or serum surrogates (127, 128). Intrinsic susceptibility weighted or blood oxygenation level dependent MRI (BOLD), exploits the difference in magnetic susceptibility of oxyhaemoglobin and deoxyhaemoglobin to generate contrast and identify regions of hypoxia (129).

Visualization of tumor blood flow can be used as a surrogate to identify areas of hypoxia. DCE enables *in vivo* assessment of tumor blood flow and permeability using paramagnetic contrast agents. DCE has been shown to have ability to predict treatment response in MIBC following chemotherapy (130). Experimental models demonstrate the potential effectiveness of hypoxia informed boost dose delivery to increase tumor control (126). Future partial bladder radiotherapy approaches could therefore inform a mpMRI derived biological target volume. Given this volume is up to 45% smaller than an anatomically defined bladder GTV, it opens the possibility of further normal tissue sparing (131). As the volume of radiation influences the immunogenic potential of the tumor microenvironment, defining alternative meaningful target sub-volumes particularly with systemic immunotherapy warrants further evaluation (132, 133).

CONCLUSION

MRgRT heralds a paradigm shift for bladder cancer patients with potential gains to be had at the simulation, treatment delivery, and response assessment stages. Whether the closer integration of MRI into the bladder patient radiotherapy pathway translates into clinical gains for our patient population is still yet to be determined. A framework for clinical evaluation of MR-Linac technologies has been suggested (134, 135). We would strongly advocate participation in clinical trials to generate robust evidence base to prove our expectations (and hopes) of further improving bladder cancer patient outcomes with MRgRT.

AUTHOR CONTRIBUTIONS

All authors meet at least of one the criteria recommended by the ICMJE. SH wrote the first manuscript draft. AH, BT, AB, IH, HM, CN, RS, and GS were all sub-section contributors. All authors contributed to the article and approved the submitted version.

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REVIEW
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MR-Guided Radiotherapy for Brain and Spine Tumors

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MRI is the standard modality to assess anatomy and response to treatment in brain and spine tumors given its superb anatomic soft tissue contrast (e.g., T1 and T2) and numerous additional intrinsic contrast mechanisms that can be used to investigate physiology (e.g., diffusion, perfusion, spectroscopy). As such, hybrid MRI and radiotherapy (RT) devices hold unique promise for Magnetic Resonance guided Radiation Therapy (MRgRT). In the brain, MRgRT provides daily visualizations of evolving tumors that are not seen with cone beam CT guidance and cannot be fully characterized with occasional standalone MRI scans. Significant evolving anatomic changes during radiotherapy can be observed in patients with glioblastoma during the 6-week fractionated MRIgRT course. In this review, a case of rapidly changing symptomatic tumor is demonstrated for possible therapy adaptation. For stereotactic body RT of the spine, MRgRT acquires clear isotropic images of tumor in relation to spinal cord, cerebral spinal fluid, and nearby moving organs at risk such as bowel. This visualization allows for setup reassurance and the possibility of adaptive radiotherapy based on anatomy in difficult cases. A review of the literature for MR relaxometry, diffusion, perfusion, and spectroscopy during RT is also presented. These techniques are known to correlate with physiologic changes in the tumor such as cellularity, necrosis, and metabolism, and serve as early biomarkers of chemotherapy and RT response correlating with patient survival. While physiologic tumor investigations during RT have been limited by the feasibility and cost of obtaining frequent standalone MRIs, MRIgRT systems have enabled daily and widespread physiologic measurements. We demonstrate an example case of a poorly responding tumor on the 0.35 T MRIgRT system with relaxometry and diffusion measured several times per week. Future studies must elucidate which changes in MR-based physiologic metrics and at which timepoints best predict patient outcomes. This will lead to early treatment intensification for tumors identified to have the worst physiologic responses during RT in efforts to improve glioblastoma survival.

Keywords: glioblastoma, brain and spine tumors, MRI, MRgRT, radiotherapy, pseudoprogression

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INTRODUCTION

Despite the potential of Magnetic Resonance image guided Radiation Therapy (MRgRT) to treat brain tumors, a recent review (1) highlighted that only one out of twenty recent studies used MRgRT to treat brain tumor patients (2). This is because MRgRT has been almost exclusively applied to treat moving tumors located in the torso, such as in the lungs (3), breast (4), pancreas (5, 6), liver (7), prostate (8) and pelvis (9). Tumor and healthy tissue in these regions can move significantly between or during treatments due to physiological motion such as respiration (3, 10, 11), digestion (12), and involuntary movements (13). Additionally, target geometry may change during treatment from tumor growth or shrinkage or patient weight loss or gain. Therefore, MRgRT has been applied to detect and compensate motion, as well as detect and compensate for daily anatomic changes with rapid radiotherapy (RT) plan updates. These implementations of MRgRT are commonly termed "adaptive radiotherapy" and are available within existing MRgRT products. Since this existing workflow adapts to anatomy, we propose that these techniques be termed "anatomic adaptive radiotherapy."

MRI can also provide physiologic information such as tumor cellularity, vascularity, and metabolism that correlate with radiotherapy response. For example, changes in regional water mobility are detectable by diffusion weighted imaging (DWI) and are associated with increased cellularity (tumor growth) or necrosis (14, 15). Increased blood volume and flux (16) can be estimated from perfusion MRI and correlate to tumor oxygen consumption (16). Tumor extension and aggressiveness are also associated with its metabolic profile and can be estimated by magnetic resonance spectroscopy (17) (MRS). Among others, these techniques are collectively termed multiparametric MRI (mpMRI). Since changes in mpMRI during RT correlate with eventual tumor response (18–20), there is significant interest within the MRgRT community in adapting RT to mpMRI findings (21). For example, if mpMRI demonstrates that a tumor is increasingly cellular, metabolic, and angiogenic during treatment (i.e., resistant to standard therapies), should RT dose-escalation or other additional therapies be considered? When adapting RT to changes in tumor physiology, these applications can be called "physiologic adaptive radiotherapy" (PART).

Studies of physiologic changes during fractionated RT are not currently widespread because it has never been feasible before MRgRT systems to obtain mpMRI on a daily basis. It has been very difficult to obtain image data weekly due to the cost and logistics of scanning RT patients every week on diagnostic MRI scanners. Therefore, existing data of mpMRI during RT has been limited to a small number of institutions and patients and a limited number of time points (typically once or twice during a 6-week course of RT). While this data has been promising, MRgRT devices allow the possibility of obtaining mpMRI with high frequency throughout treatment to elucidate trends in tumor physiology that can be leveraged to make adaptive treatment decisions. With this in mind, this review discusses the potential use of anatomic and physiologic adaptive radiotherapy for treating brain and spine tumors with an emphasis on glioblastoma.

ADAPTIVE RADIOTHERAPY FOR BRAIN TUMORS

Intrafraction motion is typically not a major concern for brain tumors given the use of thermoplastic masks to immobilize the patient's head and negligible physiologic motion. However, interfraction changes in tumor size can be problematic in numerous scenarios. For example, certain tumors can have rapid cyst expansion, which has been most commonly described for craniopharyngioma (22). This leads to a recommendation for weekly or bi-weekly diagnostic MRI to ensure appropriate target dose coverage and adapt RT plans offline to anatomic changes if needed. While it has not yet been reported in the literature, cysts can be monitored on an MRgRT system and RT can be adapted easily without requiring standalone diagnostic MRIs. Additionally, edema and resection cavities are visualized with default imaging on the initial version of the 0.35T MRI system (2). For example, at University of Miami during a course of conventionally fractionated RT we have used scans obtained with MRgRT to identify or rule out serious pathologies in patients with headaches during treatment, identify edema increase or decrease during RT, and reassure patients, manage steroid doses, or consult neurosurgery based on findings (e.g., **Figure 1A**).

Glioblastoma

Glioblastoma is the most common cancer originating in the brain with ∼12,000 new diagnoses per year in the U.S.A. and median survival about 18 months (23–25). First-line treatment for glioblastoma includes biopsy or resection followed by 6 weeks of RT with concurrent temozolomide chemotherapy and 6–12 months of continued temozolomide (26). Clinically, MRI is obtained before RT for planning and then 1 month after RT to assess early response, usually an interval of ∼3 months.

Anatomic Changes in Glioblastoma During RT

T1 post-contrast and T2-FLAIR images are typically used for determining tumor response to treatment, most commonly by applying criteria specified by Response Assessment in Neuro-Oncology (RANO) (27). Up to 49% of patients with glioblastoma demonstrate growth on T1 gadolinium-enhanced MRI acquired after the 6 weeks of standard chemoradiation treatment (28, 29). Patients with true progression of non-responding tumor continue to progress on serial MRIs and often die within 9 months (30–32). Some patients with growth on MRI after chemoradiation will stabilize or spontaneously regress without treatment modification, a condition termed pseudoprogression (30–32). This condition reflects therapy response with recruitment of blood vessels and/or necrosis and improved median survival ∼38 months (28, 33). Unfortunately, no current technique reliably distinguishes true progression and pseudoprogression when these changes are present within the

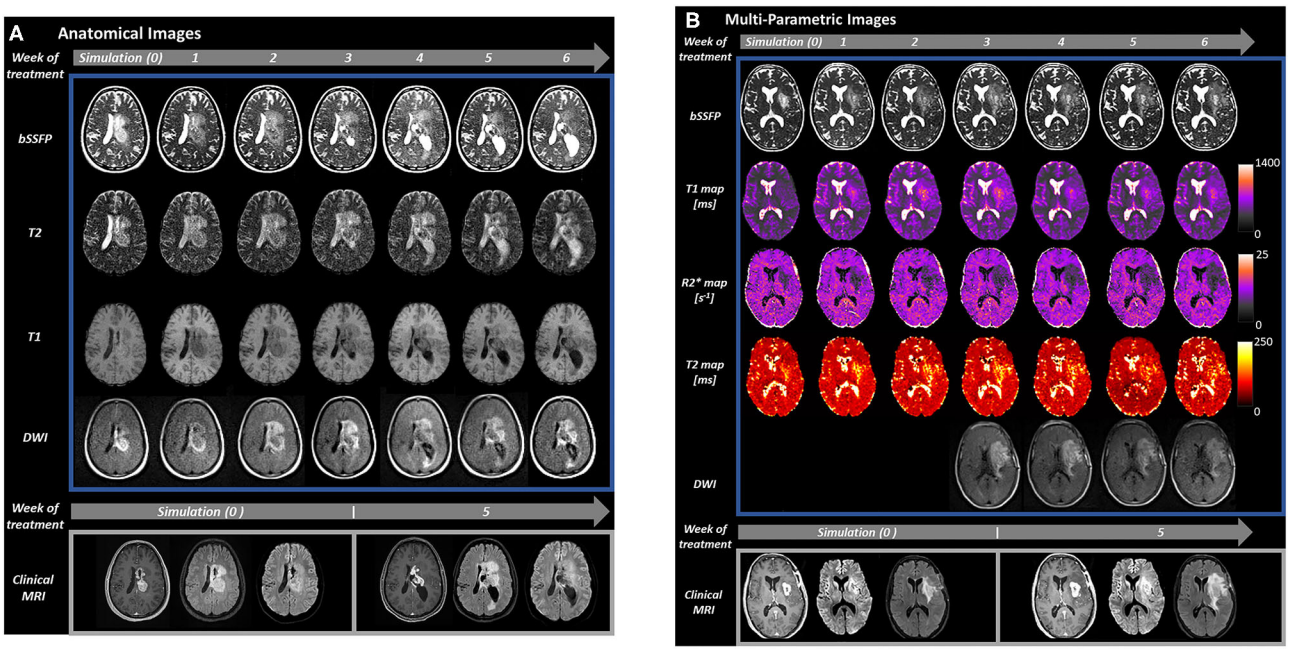

FIGURE 1 | Serial MRI of two patients with glioblastoma acquired during MRgRT on the 0.35 T MRIdian (Viewray, Cleveland, OH) combination MRI and RT system at the University of Miami (top of image, blue rectangle). Imaging was obtained at simulation (week 0) and daily on MRIdian through the course of treatment, though shown weekly for simplicity (gray arrows with treatment week number). Our MRIdian workflow for glioma patients includes 20 min for daily patient setup and intensity modulated RT which includes whole brain highly T2 weighted bSSFP (1.5 × 1.5 × 1.5 mm, 128 s) for positioning, 3D couch shifts applied by the therapist analogous to non-MRI guided RT systems, and cine MRI during RT for position verification through treatment. RT is then followed by 15 min per day of additional mpMRI imaging with the patient in the same position for a total daily time of about 35 min. Comparison images are shown for each patient from a 3 T Skyra (Siemens, Erlangen, Germany) clinical scanner (bottom of image, gray rectangle) during simulation and at week 5 (RT fraction 21) of treatment. **(A)** Anatomical images (bSSFP, T2, T1, and DWI) from a 29 year old woman with a centrally located glioblastoma (IDH-1 and IDH-2 mutations negative, MGMT non-hypermethylated, H3K27M mutation negative). The patient underwent biopsy 2 weeks prior to simulation, started RT 1 week after simulation, and received 6 weeks of radiation therapy to 60 Gy in 30 fractions on the MRIdian system with concurrent temozolomide. At the bottom of the figure, the clinical scans from the left to the right-hand side are T1 post-contrast, T2 FLAIR and DWI, respectively. During week 3 of treatment, the patient's left temporal lateral ventricle became obstructed by growth of the centrally located tumor and progressive enlargement was observed. The patient became symptomatic during week 4 with headache and nausea that was controlled with dexamethasone 2 mg twice daily. After consultation with neurosurgery, the patient's radiation therapy and chemotherapy course was completed without additional intervention. The gadolinium enhancing tumor at fraction 21 had grown 7 mm outside of the gross tumor volume defined at simulation. **(B)** Multi-parametric images of a 58 year old woman with partially resected glioblastoma (IDH-1 R132H wildtype, MGMT non-hypermethylated) of the left temporal lobe with unresected portions extending into the left basal ganglia and corona radiata as shown. From top to bottom, bSSFP, T1, R2*, and T2 maps, and DWI are presented. DWI data was not available on our MRIdian system until the third week of treatment when it was added to our acquisition protocol every other day. On the bottom of the image, comparison 3 T scans at simulation and week 5 (fraction 21) from the left to the right hand side are T1 post-contrast, T2 FLAIR and DWI, respectively. This patient had progressive growth throughout treatment that was particularly prominent on fraction 21 T1 post-contrast scan (enhancing gross tumor volume margin growth of 8 mm) and R2* mapping.

radiotherapy field. Therefore, RANO criteria suggest follow-up imaging over the next 3–6 months to assess whether changes spontaneously resolve without modification of therapy or continue to progress.

Consistent with these well-known changes, a recent series of 14 patients treated with MRgRT identified T2-weighted volume increases >25% in 4 patients who had been scanned daily during RT treatment delivery (34). Most growth occurred late in treatment for three of the four patients, a previously unreported finding that could hold prognostic significance. Another study observed meaningful tumor dynamic changes during chemoradiation therapy by analyzing T1 post-contrast and T2-Flair images of 62 patients with glioblastoma (35). Since the amount of gadolinium enhancement is the primary metric used currently to evaluate glioblastoma evolution, a challenge to the MRgRT community in evaluating glioblastoma changes during RT is when and how often to administer gadolinium contrast during RT; or whether to use alternative measures of tumor growth. While it is unclear whether frequent gadolinium poses risks to non-allergic subjects with normally functioning kidneys, there is significant concern about potential gadolinium deposition in the brain due to repeated administrations and unclear symptoms that may associate with gadolinium (36).

Multiparametric MRI of Glioblastoma for Response Assessment

Existing data suggests that there is an evolution in tumor physiologic changes that occur in glioblastomas during RT. Different MRI contrasts such as T1-weighted (37), T2-weighted (38), Perfusion (39), Diffusion Weighted Imaging (DWI) (40) and proton Magnetic Resonance Spectroscopy (MRS) (41) have been investigated for early detection of glioblastoma response to

treatment. Many of these techniques have been implemented or are in development on MRgRT devices, and an example is given in **Figure 1B**.

T1 and T2 and Quantitative Multi-Parametric Mapping MRI

Spin-lattice (T1) and spin-spin (T2) relaxations are mechanisms intrinsic to the tissues and measurable by MRI. The different rates of relaxation can be mapped, and quantitative measures of MRI changes can be provided. For example, quantitative multi-parametric mapping (qMPM) is a technique to obtain multiple MRI parameters in a short amount of time (42). This technique has allowed for fast and accurate mapping of different relaxation parameters such as R1 (1/T1), R2* (1/T2*), and R2 (1/T2) and their association with glioblastoma diagnosis. A previous study showed that R1 and R2 maps identify shorter relaxation times for voxels closer than further from the tumor, which was suggested to reflect tumor invasion (43). Other studies have shown promising results for using qMPM to detect sites of future tumor progression (44) and to early detect tumor progression in patients undergoing treatment with bevacizumab (45).

There may be some benefit of these quantitative measures in assessing glioblastoma response. A recent study showed the feasibility of applying the Strategically Acquired Gradient Echo (STAGE) (46) to obtain R1, R2*, and Proton Density (PD) maps in patients with GBM after each fraction by using the 0.35T MRI-linac system (47). Another study used MR fingerprinting to obtain these maps using the 1.5T MRI-linac system (48). The capability of observing tumor response to treatment via its size and relaxation time variations over the course of fractionated RT is an important step toward using MRgRT to adapt glioblastoma radiation treatment.

Perfusion

There are two main methods for measuring perfusion with gadolinium using MRI: Dynamic Susceptibility Contrast (49) (DSC) and Dynamic Contrast Enhancement (50) (DCE). DSC is based on detecting T2* signal loss due to susceptibility effects from the passage of a bolus of gadolinium contrast agent (51). This method is used for estimating hemodynamic related parameters of relative cerebral blood flow (rCBF) and relative cerebral blood volume (rCBV) (52, 53), which are reported as the most sensitive parameters for differentiating tumor progression from pseudoprogression after RT (54). Multiple post-RT studies have shown that tumor progression is associated with higher values of rCBV in comparison to pseudoprogression (19, 55, 56). Alternatively, DCE parameters are obtained by detecting signal increases from dynamic acquisition of T1-weighted images during a gadolinium bolus passage (57). The resultant signal changes are used to estimate parameters such as area under the curve (AUC) and volumetric transfer constant (K^{trans}), fractional blood plasma volume (Vp) and extracellular volume (Ve) (58). The K^{trans} and AUC are the DCE-derived parameters consistently reported to be higher for recurrent gliomas when compared to radiation necrosis and pseudoprogression (59–61).

MRI perfusion derived parameters have been shown to change due to chemoradiation treatment and correlate with eventual patient outcome (62, 63). For example, CBF and K^{trans} increased 30 and 10%, respectively, when DSC and DCE data from 2 weeks after treatment completion were compared to pre-treatment data (16). Larger increases were associated with shorter patient survival when compared to patients showing smaller CBF and K^{trans} changes (16). In another study, reduction in CBV post-treatment was associated with doubling of patient survival compared with patients showing increased CBV (19). Other DCE-based parameters have also been shown to change significantly due to treatment. For example, a larger decrease on volumetric plasma volume 90th percentile histogram ($VP_{90\%}$) of DCE data acquired before and after treatment was associated with pseudoprogression when compared to true progression (−39.6 vs. −2.6%) (60). Changes in perfusion parameters have also been reported for data acquired during chemoradiation treatment. For example, patients showing tumor progression presented a significantly reduced rCBV during week three of treatment when compared to pseudoprogression patients (64). Another study acquired perfusion data weekly during chemoradiotherapy to evaluate tumor perfusion response to antiangiogenic therapy during a clinical trial (65). The MRI-linac systems can provide frequent data for evaluating perfusion parameters more frequently over the course of radiotherapy. Alternatives to gadolinium such as arterial spin labeling (ASL) (66) and intra-voxel incoherent motion (IVIM) (67) may be promising to evaluate survival of patients with gliomas (68, 69) and even daily measurements during RT to evaluate tumor response may be possible on MRI-linac systems without the added risk of exogenous contrast.

Diffusion

Diffusion weighted imaging (DWI) is an MRI modality capable of measuring the apparent diffusion coefficient (67) (ADC), an estimate of Brownian motion of water molecules within an imaging voxel. Water molecules in the intra-cellular environment experience a highly restricted environment, while water molecules present in the extra-cellular environment experience relatively unrestricted diffusion (70). Thus, low ADC correlates with areas of high tumor cellularity (71, 72) and aggressiveness (14, 73).

Changes in tumor ADC during post-treatment follow up images is also capable of differentiating true progression from pseudoprogression and radiation necrosis (15, 74). The rationale is that while tumor growth increases cellular density and decreases regional water mobility, a successful treatment causes the breakdown of cellular membranes of the tumor, decreases regional cellular density, and increases water mobility (18, 75). For example, Elson and colleagues reported the potential use of ADC as an early marker for responsiveness to treatment of glioblastoma. The authors analyzed ADC values from voxels within the T2/Flair volume from 52 patients and verified that elevated minimum and mean ADC values are significantly correlated to Progression Free Survival (PFS) and Overall Survival (OS) (75). Additional metrics derived from DWI such as fraction, linear, planar and spherical anisotropy have also been reported to distinguish true progression from pseudoprogression (74).

The observation of ADC over time is the base for functional Diffusion Mapping (fDM) (76), a biomarker discussed as an early detector of tumor response to treatment and survival rate (14, 77–79). For example, a previous study analyzed DWI data from 60 patients undergoing concomitant RT and temozolomide (18). The authors generated fDM maps using data acquired before, 3 and 10 weeks after the start of treatment. In their results, they showed that patients with increasing number of high ADC value voxels during treatment have a longer survival rate when compared to patients with increasing number of low ADC voxels (52.6 vs 10.9 months). The fDM technique depends on several variables related to the ADC maps generation and evaluation, such as the metric chosen and thresholding for classifying voxels showing significantly increased, decreased, or stable ADC values over time. Although previous studies showed that all of these concerns can be overcome (80), the choice and number of measurement points has still been challenging, among other reasons due to scanning time availability and patient tolerance of standalone MRIs. A practical benefit of daily MRgRT is daily mpMRI to identify the best time points for comparisons or identify trends as well as consistent scanner parameters across centers.

A longitudinal evaluation of ADC maps obtained during fractionated therapy of head and neck tumors was demonstrated by Yang et al. using the 0.35T MRI-linac system (81). The group showed that the ADC values from a ROI within responding tumor increased consistently during treatment, while the ADC values from a volume not treated (brain stem) stayed the same. We believe that further studies should be done to evaluate the feasibility of obtaining more complex DWI-based maps such as fDM and fractional anisotropy using the MRI-linac systems to show tumor early response to treatment and allow for early planning adaptation.

Spectroscopy

Proton magnetic resonance spectroscopy (MRS) is a non-invasive method capable of estimating the concentration of different tumor-related metabolites in the brain (82). High ratios of Choline (Cho)/N-acetyl-aspartate (NAA), Cho/normalized Creatine (nCR), Cho/normalized Choline (nCho) are known to correlate with tumor grade (83). Specifically, Cho correlates to Ki-67 index, which reflects tumor proliferation of gliomas (84, 85). A high ratio (Cho)/(NAA) has been reported as a biomarker of tumor presence and is useful for delimitating glioma extension and infiltration using MRS (17, 86, 87) and MR spectroscopic imaging (MRSI) (88, 89). Given the known correlations of MRS with tumor aggressiveness and cellularity, MRSI has been integrated into the RT planning workflow in one study to select areas for dose escalation (90). Other metrics such as the choline-to-NAA index (CNI) are also commonly investigated as potential predictors of patient outcome (41).

MRS has also been applied to detect changes of metabolites during radiotherapy treatment and to associate them with patient outcome. A previous study reported that patients showing large decreases of normalized Cho from the fourth week of treatment to 2 months post-treatment correlated with a worse median OS and PFS than patients not showing such decreases (91). Another study compared MRS data from pre-RT to data from the third week of treatment and showed that patients with stable or decreased median or mean Cho/NAA ratio showed less risk of tumor progression than patients presenting increased Cho/NAA ratios over the same period (20).

We believe that the implementation of MRS sequences is technically viable on MRI-linac devices to measure metabolism during therapy. However, to the best of our knowledge it has not been done. Such implementation would allow for a more frequent evaluation of metabolites throughout chemoradiation treatment to associate early glioblastoma response to treatment. For example, glutamate and glutamine (Glx) metabolism is altered in glioblastoma, and detection of Glx is facilitated at low field (92). Glx detected by single voxel spectroscopy at 0.5T had 2-fold increase of signal-to-noise compared to 1.5T in the brains of healthy volunteers due to collapse of the C3 and C4 Glx J-coupled resonances into a "pseudo-singlet" 2.35 ppm peak at 0.5T (93). Such implementations at 0.35 T would likely be with low resolution single voxel spectroscopy that could give additional information about pseudoprogression or true progression for PART. Conversely, on 3 T scanners, whole brain Cho/NAA ratio MRSI with 5.6 × 5.6 × 10 mm resolution acquired in 15 min has been integrated into RT planning and response tracking workflows that could be considered for adaptive RT (94, 95). MRSI could theoretically be acquired on a 1.5 T MRgRT system as well, though it is unclear whether Cho/NAA MRSI on a 1.5 T MRgRT system might have suitable resolution and spectral quality for adaptive RT.

Combining Different Contrasts and Modeling Radiomics

In the sections above we described results of studies associating individual MRI contrast findings to glioblastoma detection and tumor response to treatment. However, several studies showed evidence that combining different contrasts and extracting multiple parameters from MRI improves the sensitivity of predicting patient outcomes (41, 72–74). Combining radiomics metrics from multiparametric MRI to clinical variables is also an important tool for predicting tumor treatment outcome (96). This approach has also been showed to benefit from the availability of multiparametric MRI. For example, the combination of multiparametric MRI for radiomics modeling was shown to predict patient overall survival using data from before chemoradiation therapy (97). Another, study showed that combining diffusion and perfusion weighted MRI for radiomics modeling improves prediction performance when compared to a model based only on conventional MRI or clinical predictors (98). The availability of MRI data from every radiotherapy fraction allows for the inclusion of a high sampling rate temporal component into radiomics modeling.

Technical Challenges and Limitations

Another challenge for obtaining high quality images with MR-Linac systems is related to the relatively decreased signal to noise ratio when compared to images from higher magnetic fields (≥1.5T). Therefore, a compromise among temporal and spatial resolutions is inevitable. However, strong efforts are being

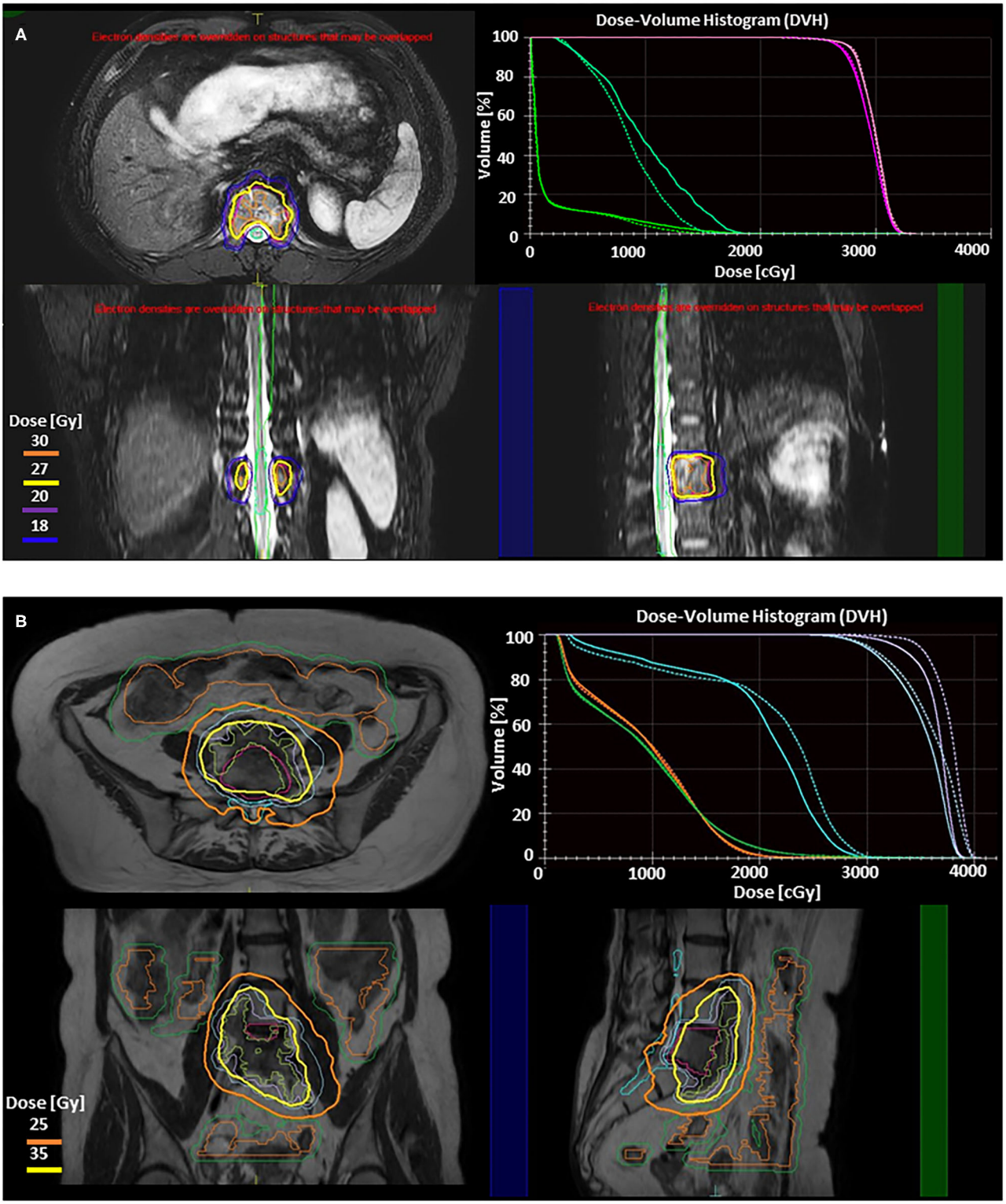

FIGURE 2 | Illustration of two adaptive approaches on the 1.5 T Elekta Unity (Stockholm, Sweden) MRgRT system for stereotactic body radiotherapy (SBRT) of spine metastases. Adapt to position (ATP) is used to correct for translational shifts by adjusting beam apertures and weights without altering reference contours. Adapt to shape (ATS) accounts for all interfraction changes by re-optimizing the plan based on the MRI of the day, and requires adjustment of the target and adjacent organ at risk (OAR) contours. These treatment strategies have been described elsewhere as well as their utilization for upper abdominal SBRT (109, 110). Real-time cine MRIs

(Continued)

FIGURE 2 | acquired in perpendicular planes through the PTV center of mass are used to monitor the target during radiation delivery. **(A)** Axial, sagittal, and coronal slices from 3D T2 fat suppressed MR images from Unity showing ATP SBRT plan to T12 metastatic thyroid lesion (GTV Pink, PTV Magenta). Prescription was 27 Gy (yellow) in 3 fractions. 30 Gy (orange), 20 Gy (purple), and 18 Gy (blue) isodose lines are also shown. DVH in right upper panel compares the reference plan (solid lines) to the adaptive plan (dashed lines). This case involves a thoracic vertebrae metastasis without any extraosseous component. The target had good separation from dose limiting organs at risk without large variations in either target or OAR position or shape, making an ATP adaptive workflow optimal as recontouring is not necessary. For ATP, after the patient is positioned on the table daily MR images are obtained, fused with the reference plan, and shifts reviewed and approved by physician prior to beginning adaptation. During the adaptive process, mpMRI can be obtained simultaneously. Once a new plan is calculated, it can be reviewed by the physician, along with a verification MR and real-time cine MRI to confirm no significant intrafraction motion. The dose volume histogram (DVH) in the right upper panel demonstrates preserved target coverage with improved OAR doses for treatment. For conventionally fractionated treatments, total time on the table for patients range from 18 to 26 min, while this patient's SBRT delivery ranged from 40 to 60 min per treatment. **(B)** Axial, coronal, and sagittal slices from T2 MR images from Unity showing ATS fraction of SBRT plan to colorectal metastasis at L5 with anterior extraosseous extension. Prechemotherapy volume (blue) was prescribed 25 Gy in 5 fractions (orange) while Post-chemotherapy volume (purple) was prescribed 35 Gy in 5 fractions (yellow). DVH in right upper panel compares reference plan (solid lines) to the adaptive plan (dashed lines), demonstrating isotoxic treatment to the cauda (teal), small bowel (orange), and small bowel PRV (green) while improving coverage to both target volumes. Here the target is within close proximity to both large and small bowel. Here we use the ATS approach, with a unique parallel contouring work flow that has been described elsewhere (111). The target was rigidly fused on the daily MR, but bowel contours were different for each of five daily fractions, requiring recontouring. This allowed for maintenance of target coverage without violation of OAR constraints. ATS workflows take longer due to time required for recontouring and adapting the reference plan to not just translational shifts but new relative anatomy. For this patient the total table time ranged from 59 to 70 min.

applied toward developing and improving data acquisition and reconstruction strategies, such as parallel imaging and non-cartesian k-space trajectories (99). Such strategies provide for fast k-space data sampling and allow more averages of the object being imaged, resulting in higher SNR images than those obtained from standard approaches. Additionally, model-based reconstruction frameworks, such as motion-corrected and high-resolution anatomically assisted (100) and image quality transfer (101) also have been shown as alternatives for improving spatial resolution of low-resolution images.

Finally, MRgRT allows for MRI acquisition while dose is delivered, which may allow for the observation of tumor changes within a single RT fraction. For example, MRI thermometry could be used to verify tumor heating during RT with hyperthermia (102) or blood oxygen level dependent MRI could monitor the increased blood flow to tumors that occurs with carbogen inhalation (103). Such approaches may be challenging, as temporal signal variances detected during radiation delivery can be related to magnetic field drifts and susceptibility artifacts due to multi-leaf-collimator movements (104).

STEREOTACTIC RADIOTHERAPY OF BRAIN AND SPINE METASTASES

The anatomic and physiologic adaptive radiotherapy discussed above might also be applied to short courses of radiotherapy (1–5 fraction over up to 2 weeks) commonly used in brain and spine metastases (105). In resected brain metastases, significant volume changes can happen if radiotherapy must start soon after resection (106). For example, one study showed that 9 out of 22 patients required treatment adjustments based on repeat MRI within 7 days after planning MRI and 7 out of 9 patients required adjustments in between 8 and 14 days after planning MRI (107). This suggests that anatomic adaptation might be helpful for longer fractionated courses. In the spine, bowel can migrate close to tumors within vertebral bodies, requiring anatomic adaptation to avoid mobile bowel on a daily basis (108). Examples of the anatomic adaptive workflows of MRgRT are shown in **Figure 2**.

While these short courses give a limited amount of time for physiologic adaptation, studies have shown that mpMRI changes correlate with response to treatment as early as 1 day and 1 week after treatment for animal models (112) and brain metastasis patients (113), respectively. Therefore, daily monitoring with MRgRT may allow for plan adaptation even in such cases. Despite the short treatment time, radiomics analysis of imaging features on the 0.35T MRgRT system were shown to correlate with outcome in pancreatic cancer (114).

CONCLUSIONS

Novel MRgRT systems provide the first capability to perform high frequency mpMRI during conventional chemoradiotherapy of brain tumors and provide a platform for physiologic adaptive radiotherapy. The references in this manuscript suggest that combining different MRI modalities to trend tumor volume and relaxation (T1/T2/T2* mapping), metabolism (MRS), hypoxia (perfusion), and cellular density (DWI) may permit a better understanding of glioblastoma response to treatment and enable dose escalated radiotherapy to portions of tumor responding inappropriately to treatment in efforts to improve patient survival. The anatomic benefits of MRI may also permit anatomic adaptation in several scenarios such as stereotactic brain and spine tumor courses.

AUTHOR CONTRIBUTIONS

DM, MS, and EM contributed to the elaboration of the manuscript text and figures equally. All authors equally contributed on selecting literature and topics for revision and discussion, reviewing, and organizing the manuscript.

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MINI REVIEW
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Technical Challenges of Real-Time Adaptive MR-Guided Radiotherapy

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In the past few years, radiotherapy (RT) has experienced a major technological innovation with the development of hybrid machines combining magnetic resonance (MR) imaging and linear accelerators. This new technology for MR-guided cancer treatment has the potential to revolutionize the field of adaptive RT due to the opportunity to provide high-resolution, real-time MR imaging before and during treatment application. However, from a technical point of view, several challenges remain which need to be tackled to ensure safe and robust real-time adaptive MR-guided RT delivery. In this manuscript, several technical challenges to MR-guided RT are discussed. Starting with magnetic field strength tradeoffs, the potential and limitations for purely MR-based RT workflows are discussed. Furthermore, the current status of real-time 3D MR imaging and its potential for real-time RT are summarized. Finally, the potential of quantitative MR imaging for future biological RT adaptation is highlighted.

Keywords: MR-linac, MR-guided radiotherapy, biologically adaptive radiotherapy, MR-only radiotherapy, online adaptive radiotherapy, real-time adaptive radiotherapy

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INTRODUCTION

The development of radiation therapy (RT) technology has enabled radiation oncologists to conform radiation doses to a level that was assumed to be physically impossible during the first 90 years of the field. Tumor margin prescriptions were developed to account for the differences between the radiation dose distribution and the patient's anatomy based on patient positioning errors, anatomical changes, and intrafraction motion (1). In-room imaging went a long way to reduce the margins needed to account for positioning and anatomical changes, but intrafraction motion remained a challenge due to the lack of real-time internal imaging of soft tissues (2, 3). This limitation was solved with the recent development of magnetic resonance (MR)-guided RT, defined as the integration of a radiation-delivery machine and an MR scanner (4, 5). While intra-fraction and real-time imaging became more straightforward, the improved soft tissue contrast of MR and the relatively low level of artifacts made this modality the first practical platform for adaptive RT (6–12).

While MR imaging delivers no ionizing radiation, some acquisition protocols are limited due to tissue heating, which restricts some of the real-time imaging protocols, especially for high magnetic field systems. The clearance between the patient and the machine is also smaller than for conventional linear accelerators, limiting patient positioning strategies. The impact of the main

magnetic field on the delivered radiation dose can be profound, and unlike computed tomography (CT), maintaining adequate spatial accuracy requires great care and needs to be checked routinely. Still, with all of these caveats, MR-guided RT (MRgRT) is likely to revolutionize some RT treatments, especially those that need high spatial resolution soft tissue imaging each fraction or real-time imaging for linear accelerator gating.

The aim of this review is to discuss technical challenges in the field of real-time adaptive MRgRT and to highlight current directions of research which reach out for new technical solutions to provide a basis for future clinical achievements in this field.

MAGNETIC FIELD STRENGTH TRADEOFFS

One of the more obvious differences between the commercial MRgRT systems is their main magnetic field strengths (4, 5). Current systems span the range of 0.35 to 1.5 T, inviting the question of what, if any, are the tradeoffs between the different magnetic field strengths? Radiology's history of MR imaging main magnetic field strengths may imply that greater magnetic field strengths always provide better images than can be acquired at lower magnetic field strengths. Because the images are produced by the net polarization of water protons, which is proportional to the main magnetic field, the number of protons available to produce the radiofrequency (RF) signal required for image acquisition increases with increasing field strength. All other things being equal, the subsequent signal to noise ratio (SNR) increases due to the increased number of polarized protons.

The purpose of MRgRT systems is to treat cancer, and since all commercial systems treat with x-rays, generally accepted clinical quality and accuracy specifications, e.g., established by the International Commission on Radiation Units and Measurements (ICRU), should be met, as should imaging accuracy. The core functionality of MRgRT systems is not to mimic diagnostic systems, and as such the benchmark for their imaging performance should not come from diagnostic radiology requirements, but from radiation oncology requirements (13, 14).

The requirements of dose distribution accuracy and image fidelity can be examined independently. With respect to dose distribution accuracy, the AAPM stipulates that the overall accuracy goal is that the delivered dose should agree with the physical dose to within 5%, a specification that includes uncertainties in machine calibration and dose calculation accuracy (15). While x-rays themselves are not impacted by the magnetic field, the secondary electrons are. When an external magnetic field is applied, the electrons are influenced by the Lorenz force, causing them to travel in a circle, but because of their many medium interactions, the overall paths are instead distorted in the direction of the Lorenz force. This distortion increases with increasing magnetic field. For larger radiation fields in a homogeneous water phantom, this distortion affects only the lateral beam penumbra. As the fields get small with respect to their secondary electron range, the entire high dose region distorts towards the Lorenz force direction (16, 17). When heterogeneities such as air cavities are encountered, the curved electron trajectories caused by the Lorentz force cause those secondary electrons to return to the exit cavity surface, substantially increasing the dose at those surfaces. These surfaces include tissue-air interfaces (such as bowel gas, the trachea, or nasal cavities) and tissue-lung interfaces, and the dose hot spots can be as large as 48% for a 1.5 T MRgRT system (18). State-of-the-art dose calculation software utilizes Monte Carlo transport calculations that model the influence of the magnetic fields, so the calculated dose can meet the accuracy requirements for a static patient, but changes in the heterogeneity distribution between the simulation scan and the patient's anatomy during the treatment can cause the doses at these interfaces to differ substantially from the calculated doses. That said, the relative dose heterogeneities can be somewhat compensated by overlapping beams from different directions. Finally, exit skin dose can exhibit the same behavior as internal heterogeneities, causing the skin exit dose to considerably higher than it would in a non-MRgRT treatment (19, 20).

Importantly, radiation dosimetry of air-filled ionization chambers is significantly influenced by the presence of a static magnetic field. To account for this effect during absolute dosimetry, dedicated field strength and chamber type and orientation specific correction factors need to be identified *via* measurements or simulations (21–25).

The imaging fidelity can be summarized as image quality for organ delineation, and geometric accuracy. It is generally considered that MRgRT systems provide image quality that is adequate for its intended purpose. MR images are generated using magnetic field gradients and an assumption of the knowledge of the relationship between the magnetic field strengths and position. Errors in this relationship cause the imaged features to appear offset from their actual positions. CT-based IGRT geometric alignment specification tolerance is 1 mm (26). Published spatial accuracy of the commercial MRgRT systems show that the 0.35 T system meets the 1 mm specification within 5 cm radius from isocenter and a 2 mm specification at 17.5 cm from isocenter (27), while the 1.5 T system has a 1.1 mm maximum spatial distortion within 20.0 cm from isocenter (28, 29).

Machine-based magnetic field errors are not the only source of MR image distortion. The patient chemical makeup will also modify the local magnetic field and therefore the apparent position of an imaged structure. Such susceptibility artifacts or chemical shifts lead to shifts in the imaged positions of anatomical structures which are proportional to the magnetic field. For human tissues, these can be in the order of millimeters for 1.5 T scanners (30), while the same artifact at 0.35 T would be much lower. For specific sequences, the susceptibility artifacts can be reduced by increasing the RF bandwidth, which has the corresponding side-effect of reducing SNR, reducing, but not eliminating the advantage of the increased field strength.

Finally, the radiofrequency energy emitted by the MR scanner is absorbed by the human body, heating the body.

The term used to describe this for clinical MR scans is the specific absorption rate (SAR). The amount of heating is proportional to the square of the magnetic field strength (31), so limiting the SAR will be more challenging for the higher field MRgRT systems. Limiting the SAR may be most challenging when conducting real-time imaging for purposes of linear accelerator gating. Two of the "selling points" of MR are that it does not deliver ionizing radiation and that it can provide real-time internal imaging, so restricting this imaging due to SAR concerns would reduce the perceived benefit of MRgRT.

REAL-TIME MR AUTO-SEGMENTATION

Current clinical experience of online adaptive MRgRT shows that one of the main bottle necks is the lack of fast and accurate segmentation of MR images. As the requirement for real-time adaptive MRgRT is to robustly provide MR-based structure delineations in the order of seconds, deep learning (DL) approaches have been investigated recently by several groups (32–36). Most DL models for auto-contouring were trained so far for the pelvic region providing to generate organ structures based on MR images (32, 34). Additionally, DL concepts for contour propagation from simulation images to daily MR have been proposed recently (37). Since adaptive MRgRT is a novel clinical application, annotated MR data for model training and validation is sparse, thus alternative approaches such as cross-modality learning have been explored (38). Even though numerous challenges remain concerning real-time MR-based auto-segmentation, first investigations regarding the clinical implementation have reported fast (few seconds) and robust use in MRgRT of prostate cancer (39).

MR-ONLY PLANNING

During real-time adaptive MRgRT, treatment planning as well as dose calculation need to be conducted for every RT fraction, but a CT simulation is no longer available. Consequently, approaches for MR-based dose planning—so called MR-only planning workflows—have been proposed to support real-time adaptive MRgRT.

MR-only planning in combination with MR-simulation for RT planning without the need of additional planning CT has been previously proposed (40, 41). Early on, mechanistic models using dedicated MR sequences, such as e.g., Dixon-based sequences, were proposed to generate synthetic CT data sets based on MR imaging data (42). Alternative approaches proposed voxel-intensity based approaches to translate MR signal values into synthetic CT readings (42). Dosimetric studies analyzing the accuracy of radiation dose calculation using synthetic CT reported dose differences on the order of 0.5% relative to CT-based dose simulation (43). Today, several commercial products for synthetic CT generation are available and studies reporting first clinical experience using MR-only simulation for RT planning have been recently published (44).

Because the acquisition of dedicated MR sequences for synthetic CT determination is time consuming, online adaptive MRgRT in today's clinical practice mostly relies on extremely simplified methods to generate synthetic CT information, such as bulk density assignments to anatomical structures. This simplification may compromise the dosimetric accuracy as currently robust conversion approaches from MR to CT are lacking. To overcome this, several groups have recently proposed deep learning models for the calculation of synthetic CT data sets based on anatomical MR imaging which has shown to be a time-efficient and robust approach (45–48). Dosimetric evaluations have shown promising results in terms of dose differences of 0–0.5% (49, 50). However, online quality assurance of synthetic CT seems to be challenging and bears dosimetric risks especially when it comes to the anatomical location and electron density assignment of bony structures. The use of undistorted MR images for synthetic CT generation is crucial in the light of real-time high precision MR-guidance. Nevertheless, the use of artificial intelligence (AI) tools for MR-only workflows may open new opportunities for real-time adaptive MRgRT using hybrid MR-linacs.

REAL-TIME MRI

One of the most compelling features of MRgRT is the ability to conduct real-time imaging (51, 52). Real-time imaging provides unparalleled visualization of internal organs to enable the clinicians to monitor and ultimately limit the impact of intra-fraction motion. This motion may be due to peristalsis, bladder filling, or breathing. The MRgRT system will provide a sequence of images, typically at a few Hertz. This sequence is typically started immediately after any setup images are acquired where the tumor is identified, and the patient moved to account for relative shifts or deformations. If the motion is due to breathing, the sequence is typically visualized for a few breathing cycles to determine the amount of motion. If gating is available and desired, a gating window is defined by segmenting the target or a suitable surrogate and applying a margin to act as a gating structure. The MRgRT system then tracks that gating structure for each image frame and monitors whether the structure is within the gating window, typically to within a pre-selected percentage. Note that this process is currently 2D, due to a lack of commercially available real-time 3D imaging sequences. Recent studies however showed promising approaches towards real-time 3D MR image acquisition (53–56) and reconstruction (57).

A critical concern is the latency between the time, the images are acquired and the time the machine or operator can respond to an undesired motion. This is related to the amount of time required to acquire the image data, to reconstruct the data, and to analyze the data and determine that a significant deviation has occurred. The latter could be the time required for the system to conduct the contouring, the determination that the motion should trigger a change in machine state and implement that change (beam on or off) or the time a human operator would take to evaluate and manually change the machine state. The latency of the image acquisition step is typically assumed to be

approximately half of the image acquisition time because the image is expected to reflect the average state during the acquisition time. The remaining latency sources are functions of the hardware and software that the manufacturer employs. These times should be short, especially for free breathing motion gating, where multiple gating events will take place during a treatment.

Recent studies have shown latency times of real-time 3D MR imaging on MR-linac systems of 300–500 ms (58). Quality assurance to verify real-time interventions should be performed using a dynamic phantom that contains MR-imageable structures and the ability to do both point (ion chamber) and area (film) dosimetry. An end-to-end test of a gated treatment that uses clinically realistic treatment times and gating windows will determine if the latency significantly degrades the treatment dose accuracy (59).

ONLINE ADAPTIVE RT

With the advent of 4D-MR imaging with minimal latency times, real-time adaptive RT seems to be one of the next technological steps of MR-guided radiotherapy. Consequently, it might be possible to irradiate moving targets with highest precision using MLC-tracking based on real-time MR readings. MLC-tracking based on CBCT imaging has been proposed earlier and proven to be suitable for clinical usage (60). A major challenge of real-time adaptive RT is the methodology of real-time dose calculation or reconstruction. Fast et al. (61) proposed a tool for online dose reconstruction which determined the delivered dose based on pre-calculated dose influence data in less than 10 ms. After initial investigations of online dose reconstruction based on 2D cine MR images (62) and 3D cine MR in addition to treatment log files (63), recent studies proposed deep learning strategies to empower real-time dose calculation and motion prediction (64, 65). Even though proposed for offline planning, methods for deep learning-based dose prediction seem to be promising tools to support real-time dose reconstruction (66, 67). In the light of current trends for reduced number of RT fractions, dose adaptation and calculation based on real-time anatomical information gets more and more important.

Accurate dose assessment of fractionated RT requires deformable dose accumulation for targets and OARs. So far, no clinically usable solution has been proposed for this problem. Therefore, robust algorithms for 4D dose accumulation are required to provide precise voxel-readings of recorded, locally varying dose distributions for better TCP and NTCP estimation (68).

Nevertheless, clinical real-time adaptive MRgRT needs thorough quality assurance and testing. To date, dedicated end-to-end tests were proposed to specifically test certain aspects of adaptive MR-guided RT (7, 59, 69–71). Future end-to-end test developments may focus on ways to evaluate real-time imaging, dose calculation, and accumulation. Furthermore, mechanisms that ensure robust and safe radiation delivery need to be implemented in real-time MR guided workflows.

FUNCTIONAL IMAGING

In addition to the enormous potential of MRgRT for geometrical precision and adaptation in real-time, functional MR data has been shown by several studies to be prognostic for outcome after RT in different tumor entities (72, 73). Consequently, interventions steered by functional MR imaging biomarkers seem to be one of the most promising concepts towards personalized, biologically individualized RT. Even though prognostic information using functional MR imaging may also be gathered with state-of-the-art diagnostic MR systems which do not suffer from hardware limitations such as the hybrid MR-linac scanners (74), biological real-time adaptation such as image biomarker guided dose painting to overcome local tumor radiation resistances can only be realized on hybrid MR-linacs (75). Biological RT individualization in terms of dose adaptation based on imaging information requires the measurement of quantitative imaging biomarkers (76). Recent studies have shown that quantitative MR imaging is possible using hybrid MR-linacs (77). Diffusion-weighted imaging (DWI), for example, can be implemented such that robust quantitative diffusion data can be measured with high repeatability and reproducibility (77). A major challenge for using quantitative biomarkers in observational and also interventional multi-center MR-linac studies will be the validation of imaging protocols for reproducibility of quantitative imaging in order to prove that quantitative imaging biomarkers are comparable between centers (78). Furthermore, test-retest studies to assess the level of repeatability will be prerequisites for future quantitative imaging studies in different tumor entities. So far, most studies have focused on quantitative imaging assessments and on investigating prognostic value of DWI (72, 74, 77, 79–81). A further challenge will be the realization of functional interventions. Currently, echo planar MR imaging (EPI) techniques are mostly used for DWI even though these are known to be susceptible for geometrical distortions (82). However, dose painting based on functional MR data requires geometrical accuracy. Consequently, current research strategies in this field include investigation of alternative MR imaging techniques, e.g., turbo spin echo (TSE) based sequences such as SPLICE (83) or strategies to correct for geometrical distortions (82). Nevertheless, hybrid MR-linacs are a major technological innovation towards real-time biological adaptation of RT aiming for increasing tumor control rates in different cancer types in the future.

DISCUSSION

MR-guided RT offers high-resolution real time MR imaging before and during RT and allows thus to adapt for inter- and intra-fraction changes. Consequently, smaller target margins and potentially better organ-at-risk sparing may be possible with MRgRT, opening new horizons towards single or few fraction RT delivery (84). For real-time MR-guidance, many involved steps require automatization. Researchers in different sub-fields have started to automatize and speed-up processes using AI methods. However, to generate robust and intelligent models which can assist with

treatment decisions, large sets of curated, standardized and well documented data are needed for model training and validation.

Furthermore, there is evidence, that biological characteristics of the tumor microenvironment play an important role in terms of radiation resistance. Consequently, quantitative MR imaging biomarkers need to be identified as predictive for RT outcome, validated in phantom and clinical studies and might then in the future qualify for interventional, quantitative MR based RT studies.

Ultimately, all technical solutions developed to overcome challenges related to real-time adaptive MR-guided RT deserve intensive clinical validation before unsupervised usage in routine MRgRT.

AUTHOR CONTRIBUTIONS

DT and DL equally contributed to writing and proof-reading of this manuscript. All authors contributed to the article and approved the submitted version.

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Initial Clinical Experience of MR-Guided Radiotherapy for Non-Small Cell Lung Cancer

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Curative-intent radiotherapy plays an integral role in the treatment of lung cancer and therefore improving its therapeutic index is vital. MR guided radiotherapy (MRgRT) systems are the latest technological advance which may help with achieving this aim. The majority of MRgRT treatments delivered to date have been stereotactic body radiation therapy (SBRT) based and include the treatment of (ultra-) central tumors. However, there is a move to also implement MRgRT as curative-intent treatment for patients with inoperable locally advanced NSCLC. This paper presents the initial clinical experience of using the two commercially available systems to date: the ViewRay MRIdian and Elekta Unity. The challenges and potential solutions associated with MRgRT in lung cancer will also be highlighted.

Keywords: magnetic resonance imaging (MRI), external beam radiotherapy, adaptive, image-guided radiotherapy (IGRT), MR-guided radiotherapy (MRgRT), stereotactic body radiation therapy (SBRT), non-small cell lung cancer (NSCLC)

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INTRODUCTION

Lung Cancer in Context

SBRT plays an important role in the curative-intent treatment of medically inoperable patients with early-stage NSCLC (1, 2). Radical radiotherapy, either alone or in combination with concurrent chemotherapy (followed by adjuvant immunotherapy in eligible patients), is the curative-intent treatment option open to those with locally advanced disease (1, 2). It is therefore crucial to plan and deliver the radiotherapy using technologies that can fully optimise the therapeutic index. This can be achieved with strategies that increase the probability of tumor control, while simultaneously reducing the probability of normal tissue complications (3).

Intra-fractional anatomical changes, attributed to cardiac and respiratory motion, pose the greatest challenge for accurate radiotherapy delivery (4–6).

These changes could lead to under-dosage of the tumor and over-dosage of the organs at risk (OARs), which could lead to an increased risk of recurrence or long term toxicity (6–8). Therefore, there is a clinical need to ensure that the tumor is receiving the prescribed dose while the dose to the OARs is kept to a minimum, e.g., to reduce cardiac toxicity and its related sequelae (7–9). MRgRT has the potential to facilitate this.

The Role of MRgRT in Lung Cancer

MRgRT has a number of potential benefits which could be exploited in the lung cancer setting. The excellent soft tissue contrast of MRI may result in the improved delineation of challenging target volumes, such as those located centrally or close to and/or invading adjacent structures, and OARs (**Figure 1**) (10). MRgRT may also enable the potential for daily plan adaptation and margin reduction, which could lead to improved OAR dose sparing (11, 12). Daily plan adaptation could account for anatomical and physiological changes throughout the course of radiotherapy and thereby has the potential to improve dosimetric accuracy (12). The "beam-on" capabilities of MRgRT systems permit real-time monitoring during radiotherapy treatment. This may allow for motion mitigation by gating or tracking and therefore again may facilitate the use of smaller margins (12). MRgRT may therefore improve the therapeutic index of radiotherapy treatment for lung cancer. Another advantage of MRgRT is the ability to acquire functional imaging to assess response and to potentially permit adaptive workflows based on biological information (13).

Ongoing research should help to highlight the specific groups of lung cancer patients most likely to benefit from MRgRT. Daily adaptive SBRT continues to be investigated as an option for (ultra-) central early-stage disease (14–19). MRgRT may also prove advantageous to patients with locally advanced disease, especially in more challenging cases where other imaging modalities, e.g., CT (Computed Tomography) and 18-Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) may fail to provide enough planning information. Examples of this include the ability to better assess tumor invasion into surrounding tissue (e.g., mediastinum, chest-wall) or where the tumor is abutting collapsed lung. Isotoxic dose escalation may be another option in this patient cohort (20). Finally, oligometastatic lung cancer patients may benefit from improved target definition and treatment accuracy, particularly for sites of disease within the abdomen (21).

There are currently five different MR-radiotherapy delivery systems documented in the literature but to our knowledge, only two of these are in clinical use (22, 23). This paper will focus on the commercially available MRIdian (ViewRay Inc, USA) and

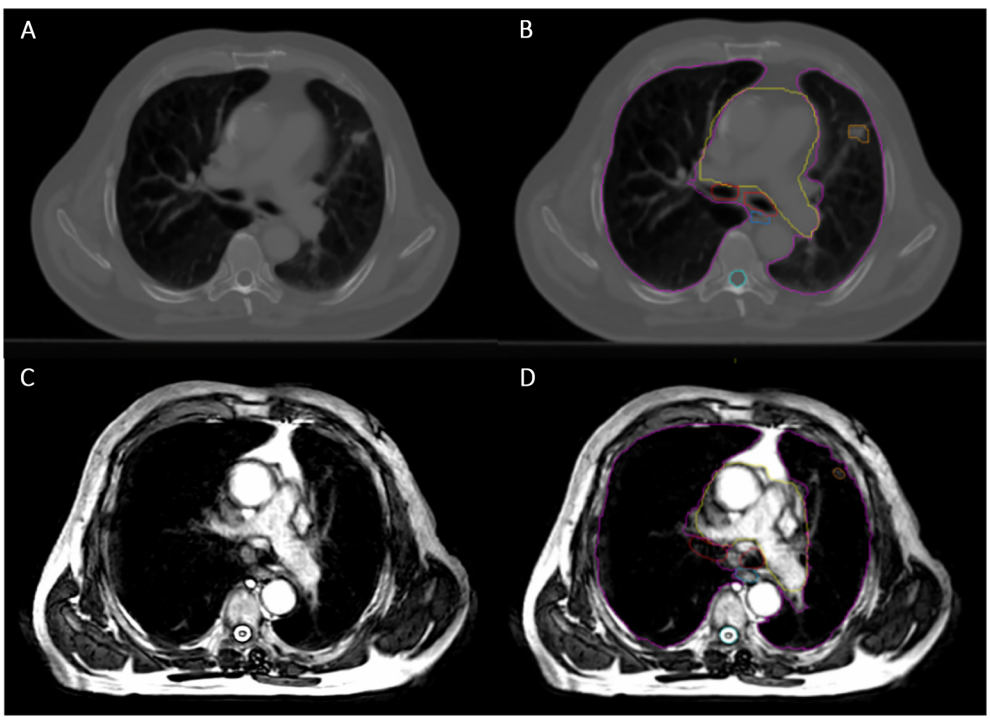

FIGURE 1 | Planning Computed Tomography (CT) image compared with MR image on the Unity. **(A)** Planning CT image showing small peripheral right lung tumor. **(B)** The same planning CT image including tumor and OAR contours (pink = lungs, yellow = heart, red = proximal bronchial tree, blue = oesophagus, cyan = spinal cord and orange = Gross Tumor Volume). **(C)** Unity MR image for the same patient, using 3D Vane – balanced Turbo Field Echo (bTFE) sequence. **(D)** The same Unity MR image including tumor and OAR contours, as described before.

FIGURE 2 | The two commercially available MR-guided radiotherapy systems. **(A)** The MRIdian (ViewRay Inc, USA). **(B)** The Unity (Elekta, Sweden).

Unity (Elekta, Sweden) systems, and their use in the lung cancer setting (**Figure 2**).

The MRIdian System

The first commercially available system, the MRIdian, was Food and Drug Administration (FDA) approved in 2012 and then introduced clinically in 2014. Initially, it consisted of a three-headed cobalt source system with a low field magnet (0.35 T) (24). The second version, which replaced the three-headed cobalt source with a 6 megavoltage (MV) linear accelerator, was FDA approved in February 2017 and the first patient was subsequently treated in July 2017 (24). There are now 34 MRIdian systems in 13 countries across the globe and to date over 10,000 cancer patients have been treated and more than 95 peer-reviewed articles have been published (25). ViewRay has also established a multicentre Clinical Co-operative Think Tank (C^2T^2) which is a collaborative group comprising clinical MRIdian users from over 20 international institutions. Its role is to enable the sharing of clinical data and best practice as well as ongoing research and evaluation of MRgRT.

The Unity System

The Unity is the second commercially available system with a magnetic field strength of 1.5 T and a 7 MV linear accelerator (24). An international consortium, including teams from seven research centers from across the United Kingdom, Europe, and the United States, was set up in 2012 to facilitate the collaborative investigation of the system and its introduction into clinical

practice (26). The first patient was treated on the Unity machine in Utrecht in May 2017, as part of a cohort of patients with spinal metastases (27). The system received FDA approval in December 2018. Currently, there are 16 Unity systems in 11 countries across the globe and to date; more than 1,000 patients have been treated (28). As of March 2020, 236 peer-reviewed publications on the development and implementation of the system have been produced (28, 29).

METHODOLOGY

A literature search was performed on PubMed to identify relevant published literature, including abstracts. It was performed initially in May 2020 but updated in October 2020. The search terms used were: ("MR-guided" OR "magnetic resonance-guided" OR MRI-guided OR "magnetic resonance imaging-guided" OR MR-Linac) AND ("non-small cell lung cancer" OR NSCLC OR "lung cancer" OR thorax OR thoracic OR lung) AND (radiotherapy OR "radiation therapy" OR SBRT OR SABR OR "adaptive radiotherapy" OR "adaptive radiation therapy" OR "image-guided radiotherapy" OR "image-guided radiation therapy" OR stereotactic). Identified articles were reviewed manually and cross-checked for other relevant papers.

INITIAL CLINICAL EXPERIENCES

Background

The initial clinical experience of thoracic MRgRT has mainly included the use of SBRT for the treatment of early-stage lung cancer (30–38). Owing to concerns relating to bronchial toxicity, SBRT use was initially restricted to those with tumors >2 cm from the central airways (15, 39). However, in recent years an increasing number of publications have shown that dose-adapted SBRT regimens can be delivered in centrally located tumors (14, 19). However, severe toxicities have been reported, particularly in patients with ultra-central tumors and prospective studies are needed in this setting (19).

MRgRT with its superior soft tissue contrast and potentially improved and adaptive planning and treatment delivery accuracy may help to reduce uncertainties and enable a reduction in planning margins and volumes (12). This in turn increases the scope for safer treatment of (ultra-) central tumors. In addition, the reduction in planning margins could make conventionally fractionated radiotherapy more attractive for patients with locally advanced lung cancer, minimising the risk of radiation pneumonitis and/or acute oesophagitis.

In Silico Studies With the MRIdian

The potential clinical advantage of MRgRT for intrathoracic disease was initially explored for SBRT of (ultra-) central tumors. A retrospective *in silico* analysis of ultra-central thoracic and abdominal malignancies demonstrated that initial treatment plans violated OAR constraints approximately 63% of the time when applied to subsequent daily fraction MR imaging (21). Online adaptive treatments (re-planning to account for anatomical changes) could have resolved all violations (21). Subsequent *in silico* retrospective analysis of hypofractionated MRgRT (12 fractions) for (ultra-) central tumors suggested a similar benefit with this approach (16).

Clinical Experience With the MRIdian

This system was first introduced clinically in 2014 and within the initial phase, 61 patients with intra-thoracic tumors were treated (30). The feasibility of MRgRT with daily online adaptive treatment for SBRT of ultra-central thoracic tumors was subsequently evaluated in a prospective Phase I study (17). Five patients were included and all received 50 Gy in five fractions. Adaptive treatments (to account for anatomical changes) were required for four out of five patients and in ten out of 25 delivered fractions. Seventy percent of the adaptive re-plans were carried out for OAR violations and 30% to improve PTV coverage. Local disease control was 100% at 6 months, with no grade 3 or higher toxicities. While patients included in this study and the two retrospective *in silico* studies had both NSCLC and oligometastatic disease from a non-lung primary, there does not appear to be any significant difference with regard to the potential benefit of adaptive MRgRT by histology (16, 21).

Other institutions have had similar clinical experiences using MRgRT to treat lung tumors (primary or oligometastases from non-lung primaries), but reports of clinical outcomes as a whole remain lacking for NSCLC (31–33, 35, 36). Adaptive MRgRT for lung SBRT was found to improve OAR sparing in 88% of treatments and improve PTV coverage compared to a non-adaptive plan in a small cohort (34). Daily adaptive MR-guided SBRT for central lung lesions was also found to improve PTV coverage in 61% of fractions with a reduction in the number of OAR violations (18).

More recently, the use of MRgRT to deliver lung SBRT in a single fraction, under real-time image guidance, has been reported (37). Re-optimised plans following on-table adaptation showed improved PTV coverage to 95% compared with 89.8% in predicted plans. Stereotactic magnetic resonance-guided adaptive radiation therapy (SMART) has also been used to treat high-risk lung cancer cases (central tumors, re-irradiation and patients with interstitial lung disease) (38). Improvements in PTV coverage were highlighted alongside low rates of toxicity and encouraging early clinical outcomes. In general, the clinical consequences of improvements in PTV coverage and OAR sparing have not been extensively reported, however.

A prospective Phase I-II trial (ClinicalTrials.gov ID NCT04115254) is currently open. It aims to evaluate the feasibility and efficacy of SMART in patients with lung, pancreatic, and renal cancer. Another institutional single-arm Phase II study with safety lead-in (ClinialTrials.gov ID: NCT03916419) is open and exploring the role of MR-guided radiotherapy in the definitive management of inoperable, locally advanced NSCLC. They are assessing the feasibility and clinical benefit of MRgRT in hypofractionated (60 Gy in 15 fractions) concurrent chemoradiotherapy and consolidation with Durvalumab is being examined.

In Silico Studies With the Unity

A study assessing the feasibility of treating nine early-stage lung cancer patients with SBRT found that clinically acceptable lung SBRT plans were possible (40). Small differences in dose to the target and OARs (especially increased dose to skin) were noted with MRgRT, but with minimal clinical impact expected. This was also found in patients with locally advanced NSCLC (20). Furthermore, the improved imaging capabilities meant that PTV margin reduction was possible, in turn facilitating increased OAR sparing and isotoxic dose escalation. A subsequent study of five patients assessed the effects of density overrides on treatment planning for MRgRT in lung cancer (41). The team concluded that when using density overrides, recalculation of optimised plans using the original CT is essential, to avoid under-dosage of the tumor.

Clinical Experience With the Unity

The Multiple Outcome Evaluation of Radiation Therapy Using the MR-Linac (MOMENTUM) Study (ClinicalTrials.gov ID: NCT04075305) has been open since February 2019. It is a prospective, multi-institutional, international cohort study/registry investigating the implementation of the Unity MR-Linac and its ongoing development. All patients treated on the MR-linac are eligible for inclusion in MOMENTUM across 12 disease sites, including lung cancer (42). The objective of MOMENTUM is to collect and evaluate technical and clinical data to allow for optimisation of software with the ultimate aim of improving local disease control, patient survival, and quality of life.

At the time of writing this paper, the Medical College of Wisconsin (MCW) has treated one patient with intrathoracic disease (inoperable stage III NSCLC) with concurrent chemoradiotherapy at a dose of 60 Gy in 30 fractions. Their radiotherapy was delivered using the Adapt To Position (ATP, virtual couch shift) workflow and was well tolerated (43).

At University Medical Center Utrecht (UMCU), 10 patients with (ultra-) central tumors have been treated thus far at a dose of 60Gy in 8 to 12 fractions. All patients were treated by daily generating a new treatment plan that was optimised to the daily anatomy visualized on the 3D MR Dataset, using an ATP and Adapt To Shape (ATS, adapted to anatomical changes) workflow (43). Treatments have been well tolerated by patients. In addition to MOMENTUM registration for MR-linac treatments, all lung cancer patients are prospectively registered in the Utrecht Cohort for Lung cancer Outcome Reporting and trial inclusion (U-COLOR). Its "Trials-within-Cohorts" (TwiCs) design enables efficient, fast, and pragmatic testing of new interventions in a randomised fashion (44).

Finally, a team in Shandong, China have treated one patient with SBRT for stage I NSCLC at a dose of 56Gy in seven fractions, with an ATP workflow applied to all fractions. Treatment was well tolerated and a follow-up CT, one-month post-treatment, showed a good local response.

Table 1 summarizes the clinical experience, to date.

CHALLENGES

The integration of MRI into radiotherapy planning and delivery systems has led to the need for changes in the radiotherapy workflow (43, 45). These changes relate to the potential for daily online imaging, plan adaptation, and re-optimisation while ensuring patients are comfortable on the treatment couch. Such workflows are still in development. The ultimate goal is to have an "MR-only" radiotherapy workflow (46). This concept incorporates MRI diagnostic scans, MRI use for target delineation ("planning MRI"), treatment monitoring and real-time adaption, and finally the use of functional MR sequences during treatment to assess for early response and enable adaptation as necessary (13, 46, 47).

Despite its potential benefits, the implementation of MRgRT into routine clinical practice has proven challenging for reasons including cost-effectiveness, patient selection, departmental logistics, changes to workflow, and technical challenges (12, 22, 48).

Cost-Effectiveness

A number of surveys on the implementation of MRgRT have indicated that health economics and/or accessibility may be the main reasons behind its slow uptake (22, 48). MRgRT systems are expensive and the delivery of value-based healthcare has been acknowledged as a global priority (48, 49). Given their expense it will be important to carefully define indications for their clinical use.

Patient Selection

Once a clinical program has been established, and the demand exceeds the MR-Linac capacity, identifying patients that will benefit most from MRgRT is crucial (48). At Washington University, a bi-weekly triage meeting has been established to review proposed treatments and help determine if and when MRgRT is appropriate based on clinical indicators and machine availability.

Departmental Logistics (Including Training)

The delivery of MRgRT requires input from a multidisciplinary team comprising physicians, radiographers, and physicists. Therefore it depends upon adequate staff resourcing, logistical co-ordination, and appropriate training (12, 23, 50). Access to multidisciplinary contour training with MRI (e.g., workshops) for staff is limited. MR contouring recommendations for GTV and OARs along with multidisciplinary training, in conjunction with a radiologist, are essential to ensure reproducibility of delineation (51, 52). MR-specific GTV and OAR contouring recommendations are currently in development.

Workflow

The use of daily plan adaptation inevitably leads to a longer clinical workflow time (23, 43, 45). As a result, the number of patients treated daily on an MR-Linac is much more limited compared to a standard linac. Overall fraction time can be further extended if the time between initial image capture and plan acceptance is too long.

TABLE 1 | Clinical experience to date, by stage.

Disease stage	Team	Machine	No. of patients	Tumor location	Fractionation schedule	Sequence used	Immobilization/ positioning	Adaption	Gating/ tracking	Couch time (min)
I/II	Thomas et al. 2018 (32)	MRIdian Cobalt-60	5	Peripheral and central	50–54Gy/3–4#	TrueFISP	NR	NR	Tracking	>20
	Padgett et al. 2018 (34)	MRIdian Cobalt-60	3 (1 primary lung)	Peripheral	50Gy/5#	NR	NR	To anatomy	NR	NR
	De Costa et al. 2018 (Abstract) (35)	MRIdian Cobalt-60	14 (11 primary lung)	NR	40–50Gy/5#	NR	NR	NR	Both	NR
	Henke et al., 2018 (17)	MRIdian Cobalt-60	5 (1 primary lung)	Ultra-central	50Gy/5#	NR	NR	To anatomy	Gating	Median = 69
	Finazzi et al. 2019 (36)	MRIdian Cobalt-60 or MR-Linac	23 (25 tumors - 14 primary lung)	Peripheral	54–60Gy/3–8#	TrueFISP	NR	To anatomy	Gating	Median from changing room to end of delivery: Cobalt-60 = 62 MR Linac = 48
	Finazzi et al. 2020 (37)	MRIdian MR-Linac	10 (8 primary lung)	Peripheral	34Gy/1#	TrueFISP	NR	To anatomy	Both	Median from changing room to end of delivery: 120
	Finazzi et al. 2020 (38)	MRIdian Cobalt-60 or MR-Linac	50 (29 primary lung)	Peripheral and central	54Gy–60Gy/3–12#	TrueFISP	NR	To anatomy	Both	Median from changing room to end of delivery: Cobalt-60 = 60 MR-Linac = 49
	Li et al., 2019 (Poster, 14th Elekta MR-Linac Consortium meeting)	Unity	1	Peripheral	56Gy/7#	T2 3D	Custom vacuum bag	ATP	Intermittent "motion monitoring"	<30
	Merckel et al., 2020 (Private correspondance)	Unity	10	Central/ ultra-central	60Gy/8–12#	T2 3D	Mattress, arms down	ATS	Nil	Median = 39
III	Straza et al., 2019 (Private correspondance)	Unity	1	Peripheral and central	60Gy/30#	4D Vane TFE	Vac fix, arms up	ATP	"Real-time monitoring"	30–35
IV	Padgett et al. 2018 (34)	MRIdian Colbalt-60	3 (2 oligo-metastases)	Peripheral and central	48–50Gy/4#	NR	NR	To anatomy	NR	NR
	De Costa et al. 2018 (Abstract) (35)	MRIdian Cobalt-60	14 (3 oligo-metastases)	NR	40–50Gy/5#	NR	NR	NR	Both	NR
	Henke et al. 2019 (17)	MRIdian Cobalt-60	5 (4 oligo-metastases)	Ultra-central	50Gy/5#	NR	NR	To anatomy	Gating	Median = 69
	Finazzi et al. 2019 (36)	MRIdian Cobalt-60 or MR-Linac	23 (25 tumors - 11 oligometastases)	Peripheral	54–60Gy/3–8#	NR	NR	To anatomy	Gating	Median from changing room to end of delivery: Cobalt-60 = 62 MR Linac = 48
	Finazzi et al. 2020 (37)	MRIdian MR-Linac	10 (2 oligo-metastases)	Peripheral	34Gy/1#	TrueFISP	NR	To anatomy	Both	Median from changing room to end of delivery = 120
	Finazzi et al. 2020 (38)	MRIdian Cobalt-	50 (21 oligo-metastases)	Peripheral and central	54Gy–60Gy/3–12#	TrueFISP	NR	To anatomy	Both	Median from changing room

(Continued)

TABLE 1 | Continued

Disease stage	Team	Machine	No. of patients	Tumor location	Fractionation schedule	Sequence used	Immobilization/ positioning	Adaption	Gating/ tracking	Couch time (min)
		60 or MR-Linac								to end of delivery: Cobalt-60 = 60 MR-Linac = 49

An effort was made to include only the most recent data to avoid duplicate reporting of patients. NR, not recorded; ATP, Adapt To Position; ATS, Adapt To Shape; TFE, turbo field echo; TrueFISP, True Fast Imaging with Steady Precession.

This is due to an increased risk of intra-fractional movement which may result in the plan no longer being acceptable for treatment (48). An increase in couch time in combination with the smaller bore size of the MR-Linac due to the presence of MR coils can lead to difficulty with patient positioning and potential patient-comfort related issues with claustrophobia, noise, feeling cold, paraesthesia, and anxiety (12, 45, 53, 54).

There are multiple steps in the process where optimisation can be implemented to reduce treatment time or improve accuracy and reproducibility of adaptive planning. One option includes the use of specialized MRgRT radiographers appropriately trained in OAR contouring to improve efficiency (12, 50). Another option may be to use auto-segmentation of OARs and even target volumes (55). Nevertheless, it is still early in the clinical implementation of MRgRT to know which interventions are most effective, so this remains an ongoing area of investigation.

Technical Challenges

MR Imaging

Obtaining high-quality MR images for thoracic radiotherapy is challenging, due to low proton density, large magnetic susceptibility differences between tissues and artefacts related to respiratory and cardiac motion (12, 48). The inability to optimise MR sequences within the MR-Linac workflow also precludes obtaining high image quality images in instances where sequences are inadequate but "locked down". Hardware differences, e.g., B_0 field strength, gradient specification, and RF coils, between standard diagnostic MR systems and MR-Linac systems, also affects image quality and the ability to acquire quantitative MR data. Both the ViewRay and Elekta systems permit diffusion-weighted imaging (DWI) to be acquired within the clinical workflow for certain treatment sites.

Electron Density Information

There is a lack of intrinsic electron density information associated with MRI. Ways of assigning CT density information to MR images include bulk density assignment, atlas-based methods or artificial intelligence approaches (56–58). The generation of a synthetic CT has been shown to work well in sites with tissue homogeneity such as prostate but its use in the thoracic region is more difficult (59). The current solution, used by the Elekta Unity system, is to use bulk density overrides of the OARs taking the mean electron density of each OAR from the CT.

Effect of the Magnetic Field

The effect of the magnetic field on dose distribution needs to be considered. The electron return effect (ERE) describes the effect of the magnetic field (Lorentz force) on secondary electrons (12, 48). The deposition of these secondary electrons at air-tissue interfaces can lead to increased doses. The ERE is reduced by modulating the treatment fields which is done as part of the Monaco plan optimisation (12). This is less of a concern with the MRIdian system due to its lower field strength (60).

Physiological Motion

The final challenge relates to the effects of cardiac and respiratory motion. The use of breath-hold imaging, respiratory gating, and 4D MRI are additional functions that would be beneficial in MRgRT for thoracic tumors (59, 61, 62). While both systems have the ability to monitor target movement (2-dimensionally) during treatment delivery, only the MRIdian can currently utilize real-time tumor imaging to modulate beam-on time during respiration. On the other hand, 4D MRI is not currently possible on either system. This may be less of a concern when 4D CT is used with initial planning for a single target such as SBRT, and especially if respiratory gating can be implemented with adaptive fractions (MRIdian only). However, in the absence of a complementary 4D CT and respiratory gating or the setting of multi-target treatment (as with locally advanced NSCLC), the lack of 4D MR imaging can pose a challenge.

An overview of the technical challenges related to MRgRT use in lung cancer has been summarized in **Table 2**, alongside their potential solutions (60, 62–64).

CONCLUSION

This review presents the initial clinical experience of MRgRT in lung cancer. The potential benefits of MRgRT for lung cancer include improved target and OAR delineation and improved dosimetric accuracy. To unlock its full potential, we will still need to overcome some technical challenges, in particular the further optimisation of motion management.

To date, most of the clinical experience gained in the lung cancer setting has been with SBRT for stage I/II NSCLC or thoracic oligometastases from non-lung primaries, including (ultra-) central tumors. Overall, there appears to be a trend toward improved dosimetric accuracy with MRgRT, however, long-term clinical outcome data is awaited.

TABLE 2 | Technical challenges and potential solutions associated with MRgRT in the thorax.

Challenge	Result	Potential solution/solution
Low proton density in lung tissue producing low MRI signal	Poor quality images resulting in difficulties with tumor and OAR delineation	Vendor provided optimised thoracic MR sequences, lower field strength, UTE sequences, hyper-polarized gas imaging or oxygen enhancement (10, 63, 64)
Respiratory and cardiac motion during image acquisition	Motion artefacts and larger planning margins	Breath hold imaging, 4D-MRI, gating or tracking (10, 62–64)
Susceptibility differences at air-tissue interfaces resulting in susceptibility induced field inhomogeneities	Reduced geometric accuracy and low signal	Lower field strength or FSE sequences (59)
Lack of intrinsic electron density information (including subsequent difficulty with synthetic CT generation)	Inaccurate electron density information leading to difficulties with dose calculation	Bulk density overrides from planning CT, research ongoing in specialized acquisition techniques, e.g., UTE sequence or the use of AI approaches (62)
Electron return effect (ERE)	Development of "hot spots" at air-tissue interfaces	Accounted for by planning algorithms or lower field strengths (60, 64)
Physiological motion during patient setup	Unrepresentative setup image	Acquire a new planning image
Physiological motion during treatment	Necessity for larger planning margins	Mid-position treatment, gating or tracking (64)

MRI, magnetic resonance imaging; OAR, organ at risk; FSE, fast spin echo; CT, computed tomography; UTE, ultra-short echo time; AI, artificial intelligence.

Ongoing clinical studies will focus on the feasibility of the definitive treatment of inoperable stage III NSCLC. In parallel, ongoing research into strategies aimed at overcoming the associated technical challenges will be required.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

CC wrote the first manuscript and sections from an Elekta perspective. PS read, reviewed and edited the first manuscript, and wrote sections relating to the ViewRay perspective. CC and PS contributed equally as first authors. DC, RC, and MD helped to design and adapted the structure of the paper from the start until the end of the writing process. DC, RC, MD, OG, SH, A-MS, MS, CR, GV, JV, and MW-W read, reviewed, edited, and wrote sections related to their areas of expertise. FM and CF-F read, reviewed, and edited the final version of the paper. GV and DC read, reviewed, edited throughout the whole writing process, and signed off the final paper. They both contributed equally to this work as last authors. All authors contributed to the article and approved the submitted version.

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Sensible Introduction of MR-Guided Radiotherapy: A Warm Plea for the RCT

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Magnetic resonance guided radiotherapy (MRgRT) is the newest face of technology within a field long-characterized by continual technologic advance. MRgRT may offer improvement in the therapeutic index of radiation by offering novel planning types, like online adaptation, and improved image guidance, but there is a paucity of randomized data or ongoing randomized controlled trials (RCTs) to demonstrate clinical gains. Strong clinical evidence is needed to confirm the theoretical advantages of MRgRT and for the rapid dissemination of (and reimbursement for) appropriate use. Although some future evidence for MRgRT may come from large registries and non-randomized studies, RCTs should make up the core of this future data, and should be undertaken with thoughtful preconception, endpoints that incorporate patient-reported outcomes, and warm collaboration across existing MRgRT platforms. The advance and future success of MRgRT hinges on collaborative pursuit of the RCT.

Keywords: MR-guided radiotherapy, RCT, evaluation, evidence, MRgRT

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INTRODUCTION

Over the past several decades, the field of radiation oncology has witnessed a range of technical innovations. We have seen paradigm-shifting advances in planning techniques, like intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT). We have also seen the introduction of particle therapy with protons and carbon ions, with the potential to better-spare normal tissues, and improved precision of radiotherapy delivery with real-time tumor tracking (1). We have witnessed the introduction and adoption of advanced image-guided radiotherapy (IGRT) (2). Many, if not all of these innovations have (partly) replaced older techniques, some with good evidence for benefit (3, 4). However, in some cases, this has been without robust clinical evidence of superiority (5).

The newest of these technical advances to reach the mainstream clinic, magnetic resonance guided radiotherapy (MRgRT), offers real-time near-diagnostic visualization of the tumor/patient anatomy (6), enabling highly accurate online adaptive radiotherapy (ART), which by adjusting the treatment plan based on the daily anatomy while the patient remains on the treatment table, improves the dosimetric therapeutic index of radiation (7). This can be through both improved

normal tissue sparing and/or accurate target dose escalation. Online ART with MRgRT has the potential to improve patient outcomes by reducing treatment-related toxicities and may enable increased local disease control through safe dose escalation. MRgRT also (presently) requires a more complex and resource-intensive workflow (8–10), with greater overall cost than standard RT.

The amount of clinical studies comparing MRgRT with CT guided radiotherapy is limited, and the number of completed or active randomized controlled trials (RCTs) even more so: in fact, we were unable to identify RCTs comparing CT guided radiotherapy with MRgRT, with the exception of one RCT in prostate cancer (clinicaltrials.gov NCT04384770.

Despite absence of strong evidence of improved efficacy, MRgRT is currently being implemented at many sites worldwide (11). In this paper, we argue that patients and societies can only truly benefit from this exciting new technology when the MRgRT community collaborates to generate solid clinical evidence, which, in large part, will require large, comparative randomized studies.

ABSENCE OF STRONG CLINICAL EVIDENCE IS BAD FOR PATIENTS

For many radiation oncologists, there is little doubt that MRgRT will improve patient outcomes. They argue that it is only logical that real-time target visualization, daily plan adaptation, and the option to accurately pause treatment during organ/tumor movement will lead to less irradiation of healthy tissue and therefore less toxicity, or better tumor control. Some would even say it is unethical to expose patients to less precise or accurate treatment in the context of a comparative study or a randomized controlled trial (RCT).

Yet, in medicine we have seen too many examples where the theoretical benefits of new treatments were not confirmed in clinical practice (12). There are also examples of promising new interventions which turned out to be harmful for patients (13, 14), or beneficial in particular settings (15) but harmful in others (16). This is even true in multiple examples where early Phase I and II clinical evidence of seemingly obvious and stepwise approaches suggested benefit (17), only to be proven wrong in RCT (18). Indeed, despite the typically promising early phase trial data that precedes an RCT, a shocking swath of Phase III oncology trials are negative according to primary endpoint (19). We should therefore pursue the highest possible level of evidence for MRgRT, and with collaborative enthusiasm.

The argument that an RCT is unethical in the setting of a "logically superior" technology also does not hold from the perspective of reimbursement and patient access to care. Although evidence is not the sole determinant of reimbursement decisions, mainstream reimbursement for a new technology is generally accelerated when high quality clinical evidence of superiority becomes available (20, 21). Reimbursement patterns in turn are related to access to particular types of care (22), as well as to outcomes of patients with cancer, even with efforts to control for comorbidities, stage, and similarly confounding variables (23, 24). Therefore, the earlier we enter or (even better) randomize some patients into control arms, the sooner many more patients may benefit when superiority is demonstrated.

Finally, from an economic perspective, it is also important to conduct high quality, randomized research. MRgRT is more expensive than most standard RT techniques, and like with any new promising technology, not all patients will benefit from MRgRT. There will be patients in whom the *a priori* risk of toxicity is so limited, that there is simply very little room for MRgRT to improve outcomes. Similarly, some patients will experience high toxicity despite MRgRT. Thus, from a cost perspective, we need to identify those patients and administer MRgRT only to patients who are likely to benefit.

WHY WE NEED PROSPECTIVE TRIALS AND RANDOMIZATION, AND NOT JUST REAL-WORLD DATA

We need to demonstrate that theoretical benefits of MRgRT translate into real benefits for patients. As of today, the RCT remains the gold standard for demonstrating superiority of new treatments. Some argue that 'real world evidence', coming from large registries, can be a good alternative to RCTs. However, evaluation of new treatments using real world data is prone to a strong type of bias, i.e. confounding by indication. This type of bias is prevented by randomization.

Confounding by indication occurs in daily practice, where patients who are referred for a new, promising and innovative treatment like MRgRT are different from patients who are not. Usually, patients with access to innovative treatment are fitter, have less comorbidity, are more educated, have healthier lifestyles, and are better informed. Superior outcomes in these patients cannot be solely attributed to the new treatment, as they may very well be the result of difference in their pre-treatment health status and prognosis. These factors are generally difficult to measure and therefore impossible to (completely) adjust for by statistical analysis. With randomization, the treatment choice is based on chance only, and is independent of patient characteristics. Confounding by indication cannot be prevented in registry studies and real-world data, no matter how matter how big or how detailed they are.

WHAT WORK NEEDS TO BE DONE BEFORE WE CAN EMBARK ON RCTs

Before a new technology like MRgRT is ready for formal comparison with the standard treatment, some preparatory steps need to be taken. A possible framework for this has been proposed is the R-IDEAL recommendations (25), based closely off of the IDEAL recommendations (26). The R-IDEAL concept describes the road towards evidence-based implementation of innovations

in radiation oncology and starts with Stage 0 (Radiotherapy predicate studies), followed by stage 1 (Idea, first in man) and Stage 2a (technical development studies), after which clinical effectiveness of the technology is evaluated in early randomized controlled trials (Stage 2b, exploration, and Stage 3, assessment), followed by long-term study (Stage 4) and surveillance.

One important step is to develop a method for proper patient selection for trial entry. Not all patients are likely to benefit from MRgRT: some may have good outcomes with standard treatment, while in others the potential gain of MRgRT is so small that it will not translate into clinically meaningful or measurable improvements. An exceptionally elegant approach for patient selection that comes from the field of proton therapy, and may be readily applicable to MRgRT, is the model-based indication (27). Model-based indication is a stepwise methodology of selecting patients for a novel therapy when the primary goal is to reduce treatment-related toxicity. This approach comprises two phases, first to select patients who may benefit from a novel technology (MRgRT for this discussion) and second, to clinically validate MRgRT through comparative studies, preferably RCTs. In the first phase, patient selection is carried out by sequentially evaluating 1) normal tissue complication probability (NTCP) estimates for tissues of interest 2) *in silico* dosimetric comparison studies using MRgRT and ART vs. standard IGRT and conventional planning 3) the estimated clinical benefit based on the NTCP risk and potential dosimetric gains (28). Then, in phase two, patients with an expected clinical benefit (based on the phase one assessed NTCP-value reduction) that meets a defined clinical threshold will be enrolled in RCTs. Although this stepwise approach to clinical trial development may seem unusually structured (and perhaps aseptic), clinical development of MRgRT requires timely identification of best applications to minimize resource waste and to maximize the likelihood of long-term success.

Another area where pre-work is needed is the field of Health Technology Assessment (HTA). With health care costs rising disproportionally in many societies, payers and policy makers are, understandably, not always overly enthusiastic to adopt or reimburse new, more expensive interventions. Therefore, we advocate for groups to perform early health technology assessment, analyses where the costs per quality of life year gained (QALYs) are calculated and compared between technologies. In these models, assumptions of effectiveness and costs are made, in order to identify areas where MRgRT has the potential to become cost effective. These models will give insight, for example, into what extent toxicity needs to be reduced in order for MRgRT to become cost effective. Or, what the maximum costs of MRgRT are allowed to be, given a certain (likely) toxicity reduction. Conclusions of early HTA analyses may have varying implications across different countries worldwide, as the threshold for cost effectiveness varies internationally. Through early identification of scenarios where MRgRT will likely be too expensive or not incrementally effective enough to be cost effective, with mindfulness of international variation in cost-effectiveness, one can redirect research efforts to more worthy tumor sites or treatment strategies.

WHAT ENDPOINTS DO WE NEED TO CHOOSE?

Choice of endpoint will depend on the stage of development of the technology. Of course, in early stages of technology and clinical development, more advantageous dose distributions, and lower dose to healthy tissues are encouraging and relevant. Smaller margins, adaptive planning, and more favorable dose distributions may indeed translate into lower toxicity of better quality-of-life. Similarly, dose-escalated treatment plans with sparing of organs-at-risk are likely to lead to better tumor control. However, we strongly believe that, at some point before widespread introduction of the technology, it is important to demonstrate that these theoretical benefits, confirmed by proxy endpoints, translate into real clinical benefits for patients. In the era of shared decision making, disease-free or progression-free survival are no longer the only or most important outcomes of interest. Neither are doctor-assessed acute and chronic toxicities.

We think that patients could, and should, play an important role in relevant trial endpoints. Also, we believe that patients themselves are in the best position to provide these endpoints. There is no one better positioned to report outcomes in the domains of physical functioning, role and social functioning, and cognitive functioning than a patient themselves. Patient reported outcomes (PROs) must be considered in MRgRT. Also, in terms of "traditional" outcomes, like measured toxicity, instead of the doctor taking a snap-shot at the outpatient clinic, we believe that toxicity and functioning are better assessed by the patients themselves at multiple time points during follow-up. Fortunately, multiple technological solutions (including established cloud-based solutions, apps, and websites) and tools (such as the validated PRO-CTCAE, EORTC QLQ-C30, and other questionnaires) are readily available (29–32). As MRgRT study designs are considered, strong consideration should be given to PRO-based endpoints as either primary or complementary objectives.

DO WE ALWAYS NEED TO DO AN RCT?

As clear as our plea for the RCT in MRgRT may be, there are clinical scenarios in which RCTs are impractical and unnecessary. One such scenario is the evaluation of late effects. It remains a challenge to establish high quality late toxicity data, particularly when toxicities occur outside of standard clinical trial windows. In this setting, large, high quality, multi-institutional registries could play a pragmatic role in capturing a diversity of potential events that could occur sporadically and take place years following treatment completion. Given the potential rarity, diversity, and variably long timeframe for late toxicities to develop, they are an impractical endpoint for the clinical development of a novel technology. We need evidence for MRgRT imminently, and choices of late toxicities as primary endpoints for initial RCTs in the field would unreasonably delay clinical development. Similarly, RCTs for rare tumor sites where

accrual is challenging and slow, remain impractical in the initial development of MRgRT. Registries may again be useful in this scenario. We would also argue that within particular body-site settings, gains through technology advances like MRgRT are often translatable across histologies. It stands to reason that if MRgRT were proven beneficial in toxicity reduction of SBRT for unresectable pancreatic cancer, it might similarly offer toxicity reduction for SBRT to a renal cell carcinoma oligometastasis to the pancreas.

Apart from late outcomes and rare cancers, it has also been argued many times that RCTs are inappropriate for "parachute" style situations. One would not perform an RCT of a parachute use vs. jumping without.

Of course, there may be individual situations where the anticipated benefit of MRGRT is too large to justify randomization. However, in general, like most medical practices, MRgRT is unlikely to present "parachute" style scenarios (33). One does not need to look far into the history of medicine to identify RCTs where the primary endpoints were thought by many to be slam dunks, but were indeed ultimately negative (34). Or, for that matter, where unexpected effects of an experimental approach decimated any benefit (35). We maintain that RCTs are the gold standard in oncology trials and non-randomized and observational studies should not be viewed as a replacement for them, but rather as a complement to them in the pursuit of MRgRT development.

CAN VARYING MRGRT TREATMENT PLATFORMS BE USED FOR A COMMON GOAL?

In the clinical mainstream of MRgRT, two MR-linacs (MRL) platforms are commercially available and in global use. They are the 1.5-Tesla (T) MRL (Elekta Unity) and the 0.35T MRL (Viewray MRIdian). Although the imaging units on board these two MRLs vary in strength, the clinical imaging utility itself is similar with regards to clinician ability to distinguish the daily anatomy, even in complex soft tissue sites like the abdomen (36). Indeed, we believe these systems are far more alike than different, especially when placed in the context of other existing linacs. We do recognize there may be particular niche applications focused on imaging endpoints that may be best performed on one platform vs the other for consistency (37). However, the broad capabilities of the MRL systems, like online adaptation (whether it is referred to as "SMART" or "adapt to shape") or MR-guided alignment and gating (MR-based setup, whether given the name "adapt to position" or not) are mainly translatable across platforms, with no greater difference than that between an Elekta Versa and a Varian Truebeam (the modern, high-throughput CT-based linacs at time of this writing). There is indeed long-standing precedent in the field of radiation oncology to permit multiple disparate technologies within a single trial, even with different imaging types, different multi-leaf collimators, and different motion management, as long as the delivered therapy is overall equivalent. To say that the 1.5T and 0.35T systems cannot be used interchangeably in a trial of online adaptation would be like saying a lung SBRT trial could only occur on a Truebeam, but not a tomotherapy or Cyberknife unit (38). Focusing on differences between MRLs, rather than similarities, will only divide efforts, attention, funding, and patient resources, and ultimately delay the success of MRgRT. Thus, RCT and other study efforts should aim to be collaborative across platforms and institutions, to maximize the timely impact of this new technology. Both platforms have formed consortia, where radiation oncologists, physicists, methodologists and other experts collaborate to work towards evidence-based implementation of the technology and optimized radiation treatment approaches to improve patients' outcomes (39). These consortia are in the excellent position to design and initiate international, platform agnostic, multicenter RCTs.

Finally, it will be challenging to find the right balance between having enough sites offering MRgRT to run RCTs, while avoiding large scale uptake of the technology withouth clinical evidence. As with many technical innovations, the time window for RCTs is narrow. We should avoid a situation where MRgRT has been implemented on a large scale, where radiation oncologists and therapists have become accustomed to providing MRgRT, and where it has become too late to de-implement the technology for tumor sites of patient categories where RCTs have not been able to confirm superiority or cost-effectiveness. Therefor, it is imperative to start RCTs sooner rather than later.

CONCLUSION

We believe that RCTs are central to the future success of MRgRT. Randomized data will help to identify and substantiate the potential clinical gains of MR-guidance, and will ensure coordinated dissemination of this novel technology. The MRgRT community needs to unite across platforms to enable thoughtful conception of randomized trials, with modern endpoints, and with timely generation of the high-quality evidence needed to support the future of the field.

DATA AVAILABILITY STATEMENTS

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

HV: Conceptualization and writing LH: Conceptualization and writing. All authors contributed to the article and approved the submitted version

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MR-Guided Radiotherapy for Head and Neck Cancer: Current Developments, Perspectives, and Challenges

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Based on the development of new hybrid machines consisting of an MRI and a linear accelerator, magnetic resonance image guided radiotherapy (MRgRT) has revolutionized the field of adaptive treatment in recent years. Although an increasing number of studies have been published, investigating technical and clinical aspects of this technique for various indications, utilizations of MRgRT for adaptive treatment of head and neck cancer (HNC) remains in its infancy. Yet, the possible benefits of this novel technology for HNC patients, allowing for better soft-tissue delineation, intra- and interfractional treatment monitoring and more frequent plan adaptations appear more than obvious. At the same time, new technical, clinical, and logistic challenges emerge. The purpose of this article is to summarize and discuss the rationale, recent developments, and future perspectives of this promising radiotherapy modality for treating HNC.

Keywords: MRI, MR-guidance, IGRT (Image Guided Radiation Therapy), head and neck (H&N) cancer, adaptive radiotherapy, xerostoma, salivary gland

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INTRODUCTION

In recent years magnetic resonance guidance (MRg) emerged as a new promising modality within the spectrum of image-guided radiotherapy (IGRT) (1), allowing for better tumor and soft tissue visualization, repetitive imaging without additional dose exposure, target volume gating, and online plan adaptation (2). Following the first platforms with these features, including low-field MR-imaging facilities and a cobalt source (3), soon the first hybrid platforms were developed combining this image modality with a linear accelerator (MR-Linacs) (4).

At present, MR-Linacs are widely used for treating various indications and tumor localizations, e.g., stereotactic body radiotherapy (SBRT) of the upper abdomen or the lung, prostate cancer, and other pelvic targets like the rectum (5). These applications are predominantly chosen due to the obvious benefits of daily plan adaptations when including target volumes and organs at risk (OAR) with distinct inter- and intrafractional motion or anatomical changes and due to the often used hypofractionated regimens limiting the efforts of repetitive adaptations (6, 7). On the other hand, implementation of this novel technology for treating head and neck cancer (HNC) remains at its

infancy, and published data about its technical and clinical applications are scarce (8) and mainly limited to MR-cobalt platforms (9). However, despite the technical and clinical challenges of HNC-radiotherapy such as long-course regimens, enhanced acute toxicity, and patient immobilization using masks compromising treatment tolerance and more complex plans with a multitude of OAR, the first research groups have already started exploiting possible benefits of MR-Linacs for this indication (10–13).

The goal of this article is to present current developments in the field of MR-guided, adaptive radiotherapy for HNC and discuss clinical benefits and difficulties of the adoption of this promising technique. For this purpose, and because of the lack of a broad consensus regarding the MRg-definition, also data and knowledge gained from MR-planning guidance before x-ray IGRT were included.

ADAPTIVE TREATMENT FOR HEAD AND NECK CANCER AND POTENTIAL BENEFITS

The concept of adaptive radiotherapy (ART) for HNC relies on accounting for potential anatomic changes during the treatment course, associated with, amongst others, tumor shrinkage, weight loss, or organ/structure migration and has been heavily exercised in the last two decades.

The original purpose of ART was to compensate for target position variability during radiotherapy in order to ensure correct dose accumulation, which led to the development of on-line 3D-imaging in the form of cone-beam-CT (CBCT) (14). Yet, most modern ART-approaches focus more on improving dose-sparing for specific OARs like the parotids (15–17). Although there is a lack of prospective clinical trials evaluating the objective benefit of ART for HNC, several dosimetric studies have been published so far, e.g., demonstrating an underestimation of the cumulative dose to the parotids when using the original non-adapted plan only, leading to increased probability for xerostomia (15, 18). Raghavan et al. were one of the first groups to demonstrate both a migration of the center of mass of the parotids, as well as a bilateral volume shrinkage in 6 HNC-patients, using an MRgRT-dedicated platform (19). An example of parotid migration and volume reduction demonstrated with the help of longitudinal imaging on the MR-Linac is shown on **Figure 1A**. An example of actual dose delivered to the parotid glands contoured offline after completion of treatment on a MR-Linac is shown in **Figure 1B** (20). Mohamad et al. showed that MRgART may be beneficial especially for swallowing related toxicities in HPV+ low risk HNC patients, especially at risk for long term toxicity due to the excellent outcome of these patients (21).

In general, the use of MRI during the course of HNC treatment is beneficial because of the superior soft-tissue contrast, thereby allowing for more precise tumor delineation and margin reduction (22). Therefore, daily online adaptive

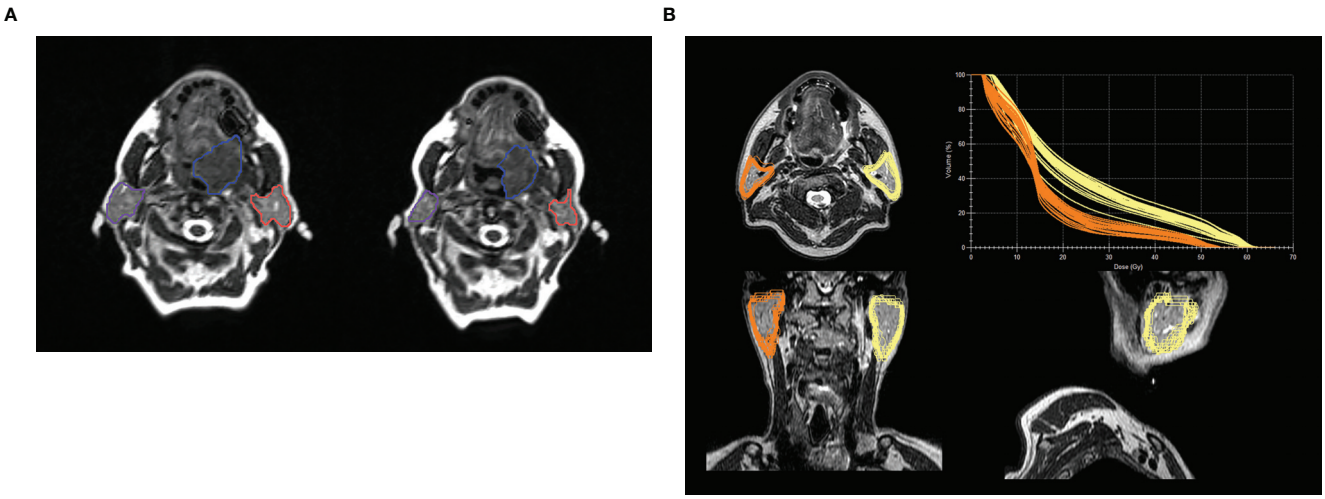

FIGURE 1 | **(A)** Example of volume changes and migration of parotid glands during the course of fractionated radiotherapy at an 0.35 T MR-Linac or a large base of tongue carcinoma between treatment start (left image) and beginning of the 7th treatment week - boost (right image). Left and right parotid glands are delineated in orange and violet respectively and the gross tumor volume in blue. The volume of the left and right parotid glands decreased by 8.2 cc and 10.0 cc, respectively. The inter-parotids distance changed from 11.0 cm to 10.3 cm. **(B)** Example of a post treatment analysis for a patient treated for a hypopharyngeal carcinoma with 70 Gy in 35 fractions. Parotid glands were contoured for each daily MRI during the course of fractionated radiotherapy at a 1.5 T MR-Linac and propagated to the T2w planning MRI, with the total plan DVH for each daily delivered plan in the upper right corner, showing the variance in actual delivered dose depending on volume of the parotid gland. Averaged D_{mean} of the anatomically corrected and daily adapted plans was 24.4 Gy and 16.5 Gy for the left and right parotid glands, respectively. The D_{mean} of the reference plan was 25.9 Gy for the left and 16.7 Gy for the right parotid gland. Baseline volume was 31.0 ccm for the right and 34.5 ccm for the left parotid gland. Mean volume (range) during treatment was 30.3 ccm (29.5–32.1) and 31.4 ccm (29.1–34.7). The example was presented as a poster at the congresses of DEGRO and AIRO 2019 by Monica Io Russo, MD (20).

MR-guided RT could potentially be beneficial for fast responding tumors, e.g., Epstein-Barr positive nasopharyngeal cancers or HPV-positive oropharyngeal cancers (OPC) (23). Also, patients with large respiration- or swallowing induced tumor motion, like in the case of laryngeal carcinoma could benefit from MRgRT (24). But, generally, anatomical changes in the head-and-neck region are slower, e.g., caused by weight loss or target volume changes. Several studies have investigated adaptive RT for head and neck treatments, but not many studies have considered this in the presence of a magnetic field. One study in 2018 has investigated plan quality after weight loss in the presence of a magnetic field (10), showing that the current approaches of offline planning once or twice per week might be sufficient for reducing the dosimetric impact of weight changes.

Besides improved soft-tissue contrast, another advantage of MRgRT is the potential for tumor response monitoring throughout treatment without additional imaging dose (25). One study from 2016 has studied the feasibility of treatment response assessment of head and neck cancer patients using diffusion-weighted (DW) MRI on a Cobalt-60 ViewRay system (26). This study showed variation in tumor apparent diffusion coefficient (ADC) values and consistent brainstem ADC values throughout treatment, potentially allowing for early treatment response assessment. Especially DWI is a promising candidate as a prognostic imaging biomarker in HNC (25, 27–31), but with still conflicting results depending on the parameters analyzed (32). Moreover, early changes in quantitative MR parameters in OAR such as parotid glands may help to predict late toxicity like xerostomia, enabling therapeutic interventions or plan adaptations (33, 34). Thus, MR-Linacs with their capability of longitudinal DWI, may facilitate a biologically adaptive treatment, depending on therapy response for tumors and/or OARs (35).

MR-GUIDANCE IN HEAD AND NECK RADIOTHERAPY: CURRENT STATE OF RESEARCH

Besides FDG-PET/CT, MRI has become an essential imaging modality in staging of HNC (36–39). Moreover MRI enables a better visualization of the macroscopic tumor for target volume definition and estimation/reduction of PTV margins during radical radiotherapy (40–42), as well as reduced interobserver variability (16, 18, 43–45), although prospective evaluation on primary outcome is lacking. Moreover, offline image registration remains a pitfall, if MRI is not performed in treatment position (46, 47). For treatment on the MR-Linac a simulation scan in RT position is readily available to overcome these difficulties and simultaneously offers one of the main benefits of these platforms.

Repetitive offline MR scans show, especially for HPV-associated OPC, a shrinkage already in the first weeks of therapy (48) up to a complete response in imaging in around 50% of the patients mid-treatment (49). Most of the existing data about MR-guidance in HNC treatment is in the setting of offline MRI, as online MRgRT is still a new development with only a handful of institutions treating patients with HNC on MR-Linacs and only limited data on feasibility of MRgRT in HNC published (8, 9). Tabular overview of published series or recruiting trials is provided in **Table 1**. With the above mentioned potential benefits for OAR sparing with ART (21) and the obvious advantage of daily MR-guided therapy at hand, a first prospective phase II trial for low risk HPV-associated OPC patients was initialized by the MD Anderson Cancer Center [NCT03224000 (50)]. In this trial, low risk HPV-associated OPC patients will be treated on the MR-Linac with a protocol based adaptation for the high dose volume depending on the shrinkage of the GTV. For adaptation to shrinkage of macroscopic disease an important issue may be the blurring of the tumor borders in MR-images, which is seen in studies of serial MRI during RT (48, 49). Because of this, there might be the necessity to include a GTV to CTV margin to account for these uncertainties, which need to be addressed in proper prospective clinical trials and *post hoc* analyses of the acquired imaging data with regimens not adapting the high dose target volume.

Several more prospective protocols are open for recruitment or will be opened soon to explore the role of MRgRT in HNC in various aspects: prospective basket trials, including various tumors and localizations, explore the feasibility of MRgRT depended on slots and patient burden, due to longer treatment time, noise, and claustrophobia (NCT04172753). Concerning clinical trials dedicated to HNC, the MARTHA-trial investigates potential benefits of weekly offline adaptation, narrow CTV to PTV margins and daily MRg-IGRT for reducing xerostomia in bilaterally irradiated patients over a conventionally fractionated, curative irradiation course of 7 weeks [NCT03972072 (13)]. Patient comfort and compliance will be also evaluated as secondary endpoints. Another trial will test the capability of SBRT in HNC for patients not fit for concomitant radiochemotherapy in combination with immune checkpoint inhibition (DEHART trial, NCT04477759). This is an intriguing approach for combined treatment, especially in HNC with a strong biological rationale, including the immunosensitizing effects of radiotherapy for this indication (51) or the interplay between hypoxia and immunotherapy (52). The number of running prospective trials for HNC cancer is limited so far and the existing studies do not implement identical approaches regarding the frequency and modality of adaptation, i.e., daily versus weekly, or online versus offline adaptive radiotherapy. Up to the present day, no results of prospective trials or registries have been published as a full paper but there were several presentations on congresses (1, 53–55).

CHALLENGES TOWARD ONLINE ADAPTATION

Although the number of patients with HNC treated in all of the commercially available MRgRT platforms is increasing worldwide, there still exist several open questions, both in terms of physics and logistics.

One technical challenge in treatments on the MR-Linac that is also relevant in HNC, is the electron return effect (ERE), caused by

TABLE 1 | Overview of published and ongoing studies on MR-linac-based adaptive radiotherapy for head and neck cancer.

First Author/PI	Year	Study design	Platform	Total patientsn	Timepoints of analysis/ adaptation	Aim	Main finding/study endpoint	Relevance
Raghavan (19)	2016	Retrospective analysis	0.35 T MRI-guided tri-cobalt 60	6	Weekly	Quantify volume changes of parotid glands and GTV	Volume decrease of 31.3% (ipsilateral) and 21.8% (contralateral) and center of mass mitigation with increased dose compared to the reference plan; GTV shrinkage of 38.7%	Possibility of underestimation of dose to the parotid glands without adaptation regarding in increased risk of xerostomia
Chen (8)	2017	Prospective institutional registry	0.35 T MRI-guided tri-cobalt 60	12	No pre-planned adaptation	Feasibility of MRg-SBRT in recurrent HNC	MRg-SBRT feasible, early toxicity within expected range	Due to MR-guidance potential to reduce margins
Chen (9)	2018	Prospective institutional registry	0.35 T MRI-guided tri-cobalt 60	18	No pre-planned adaptation	Feasibility of MRgRT in HNC	MRgRT feasible in primary treatment of HNC	Non-randomized data reporting feasibility of MRgRT in HNC with toxicity in expected range
Mohamed (21)	2018	Prospective planning study	Offline MRI	5	Weeks 2, 4, 6	Adapative RT regarding GTV shrinkage in HPV+ OPC and impact on dose to OAR	GTV shrinkage of up to 100% in primary and 80% in LN; adaptive MRgRT lowers NTCP for Dysphagia and PEG dependency, no change in mean dose to parotid glands	Structured adaptive MRgRT for low risk HPV+ OPC may decrease risk for Dysphagia/PEG dependency
Bahig (50)	2018	Prospective two-stage Phase II trial	Offline MRI and Unity	15 + 60	Weekly adaptation	Adaptive RT for GTV shrinkage in HPV+ OPC with dose reduction	LRC at 6 month	Trial aiming to show safe dose reduction with adaptive MRgRT for shrinking GTV in low risk HPV+ OPC
Balermpas (13)	2019	Prospective phase II trial (NCT04242459)	MRIdian	44	Weekly adaptation	Reduce incidence of Xerostomia	n.a.	Prospective study trying to show the potential benefit of adaptive MRgRT to reduce Xerostomia in HNC; finding new prognostic imaging biomarkers

the influence of the magnetic field on secondary electrons, which results in dose enhancement and attenuation at interfaces between high/low density and low/high density tissue, respectively (56). The effect is more pronounced at higher magnetic field strength. Although this effect is taken into account during plan optimization, air-tissue interfaces, common in HNC-targets, might change during the course of treatment, resulting in variation in dose deposition and risk of hotspots where beams traverse from tissue to air. A recent study investigated the robustness of treatment plans with varying sinus filling (10), and showed that more robust plans can be generated by optimizing with an empty cavity, since the optimizer will then take into account the ERE. A recent planning study including ten patients with hypopharyngeal carcinoma studied the possible effect of a 1.5 T magnetic field on plan quality and dose to OAR. Overall there had been no significant differences in plan quality or doses to OAR, if the plan is optimized for the presence of the magnetic field (57). Nevertheless, the mean and maximal dose to the skin and maximal dose to larynx and trachea was significantly higher, which needs to be critically reviewed, when assessing clinical treatment plans. Moreover, differences in homogeneity and conformity can be observed, when compared to standard VMAT plans for conventional linacs, with unknown impact on outcome or QoL and future trials might need to address these differences, like when IMRT was introduced (58).

Another difficulty in head and neck treatments on the MR-Linac is the limited field of view (FOV), due to the design in which the MR gradient coil is physically split to enable a radiation window. The gap allows for maximum superior-inferior field sizes at isocenter of 22 cm for the Elekta Unity, and 28 cm for the Viewray MRIdian (59). Therefore, patients with extensive, multi-level, lymph node involvement, and/or tumors of the nasopharynx/sinonasal cavities might not be suitable for MR-Linac treatments with a single-isocenter. This, however, depends on the institutional delineation protocols and applied margins, as well on individual anatomic variations. A study from Chuter et al. (60) showed that 66.3% of the HNC-patients with a three dose-level treatment plan could be treated on the Elekta Unity, using a cranio-caudal margin of 1 cm. A reduction of this margin to 5 mm could increase the number of eligible patients by more than 15%. Another recent study showed that 6 out of 110 patients were not eligible for MR-Linac treatment with a single isocenter, including two nasopharynx patients, one oropharynx patient and three paranasal sinus patients (11). The authors stated that neutral neck position, as opposed to extended neck position, is favorable to maximise the number of patients treatable on the MR-Linac. **Figure 2** depicts a real-life patient positioning for HNC treatment on both commercially available types of MR-Linacs, implementing neutral neck position and flexible receiver coils over a thermoplastic mask.

Up to this day, a planning CT is still used for routine treatments in most institutions. However, a straightforward solution for the problem of CT/MR mismatch mentioned above would be an MR-only workflow with the problem of the missing electron density information from the CT. In the adaptive online workflow of the Elekta Unity (Elekta AB, Sweden), a contour based bulk electron density override of structures such as soft tissue, bones and air

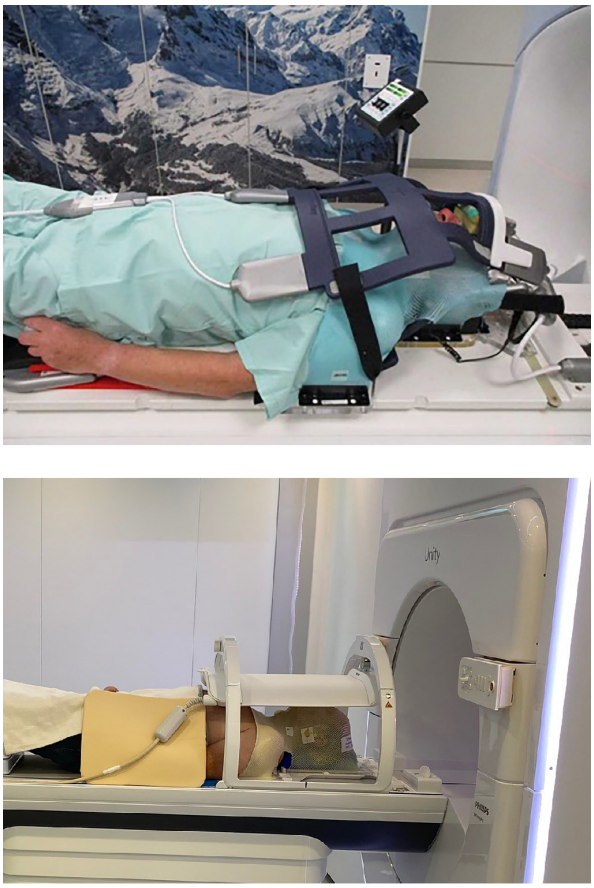

FIGURE 2 | Patient positioning for MR-Linac based treatment for head and neck cancer in the two commercially available systems.

contoured on the CT and propagated to the daily MR is provided for an online reoptimization. This delineation process is time consuming and error prone and could be overcome by the means of deep learning for bone structure delineation (61–63). When using bulk electron densities for dose calculation, the CT densities of patient positioning aids cannot be used. Therefore, all positioning devices, e.g., headrests, must be contoured with sufficient detail.

Furthermore, there is concern due to the noise for HNC patients on MR-Linacs, as headphones are not compatible with standard masks, so standard foam earplugs with the maximum noise reduction of up to 37 dB is recommended. Today, there is no prospective data published to assess the possible inner ear damage, but clinical experience for HNC patients treated in our institutions so far did not show any toxicity. To the author's knowledge, the same problem is unsolved for MR-simulations, which are routinely used in daily routine.

Finally, at the present moment, there exist several aspects that make MRgRT for HNC time consuming with currently approximately 30 min needed for applying a single fraction, and 45–50 min if online-adaptation is performed (64, 65). One of the reasons is the limited dose rate due to the larger source isocenter distance on the Unity system (5), although this is more important for SBRT with large doses per fraction compared to conventionally fractionated HNC-treatment. The dose rate of the MRIdian system is 600 cGy/minute at 90 cm SAD and such comparable to that of a conventional linac. This prolonged treatment time leads to limitations regarding the number of patients treated daily and to compliance problems over a 6 or 7 week-course of radiotherapy as is usually performed for HNC treated with curative intent. Nevertheless, some of the reasons for this time- and resource-consuming procedures could be eliminated in the near future. Both commercially available platforms (MRIdian, ViewRay Inc, Oakwood, USA and Elekta Unity, Elekta AB, Stockholm, Sweden) are only capable of delivering step-and-shoot IMRT, but there do not seem to exist any insurmountable hardware limitations for introducing dynamic MLC or VMAT (66), which will lead to significantly faster radiotherapy applications. Moreover, recent research has demonstrated that a "full" online plan adaptation does not always show significant benefits (64) and that a simple plan re-optimization is often enough for providing plans of sufficient quality (7). Applying modern developments in artificial intelligence and machine learning, in order to improve image registration and automated segmentation, could further considerably reduce time for adaptation (67).

The above facts (noise, longer treatment-time etc.) demonstrate that current practice of MRgRT is most times associated with limitations, not only of technical nature (like VMAT versus IMRT), but also with a smaller or larger compromise in terms of patient comfort. This issue becomes even more significant as most of our current treatments are applied over 6–7 weeks.

For the intriguing concept of response or biologically adaptive radiotherapy, e.g., by the means of functional imaging, several important prerequisites, like accuracy and repeatability of the measured values as well as geometrical distortions need to be taken into account. First phantom studies showed that both platforms are capable of meeting these prerequisites (24). Nevertheless, as especially the head and neck area with movement of tissue due to breathing and swallowing as well as air-tissue interfaces and the missing dedicated head and neck coils, *in-vivo* data for serial DWI on MR-Linacs acquired with the recommended procedures (68, 69) is missing (70).

DISCUSSION

Although MRgRT has advanced to an established modality for treating various tumor types, even for challenging tumor localizations like prostate cancer and moving targets like liver malignancies, implementation of this novel technique for irradiating HNC remains at its infancy. This article summarizes the most important rationales and obstacles behind this IGRT method so far and tries to present future directions of research in this quickly evolving field.

The possible benefits of adaptive MRgRT for HNC are obvious and have been exercised before with means of CT-scans, cone-beam-CT (CBCT) (16), or diagnostic MRI- (22, 45) and PET-imaging (71, 72) to serve as basis for adaptation during the

6-7 week treatment course. There are three main goals of adaptive RT cancer that can be more easily pursued with MRgRT as have been recently summarized by Corradini et al. (5): 1) adaptation to anatomical changes, 2) adaptation to tumor response, and 3) motion management. All of these issues are crucial for an effective and high-quality treatment of HNC and can be easily addressed with the new hybrid MR-Linac-platforms without additional dose exposure. The improved soft-tissue contrastation can provide -compared to CBCT- additional information not only about the external body contour and the tissue/air or tissue/bone interface, but also about relative interfractional changes of organs like the salivary glands or surgical flaps in the postoperative setting. Due to the better visualization and with more advanced adaptation algorithms and motion management strategies, classical irradiation masks may become obsolete potentially enhancing the patients comfort. First proof of principle for dedicated mask free radiotherapy planning for SRS in brain tumors showed good results for the mask free workflow (73). Furthermore, a daily monitoring of and quick reaction to tumor shrinkage, like in the case of viral-induced tumors will allow not only better sparing of OARs, but could pave the way for more elaborate dose-(des-)intensification and dose-painting trials (74), or even temporospatial fractionation approaches. Last but not least, the live, online, PTV-gating and cine-imaging allows for both 4D-planning and intrafractional motion monitoring to compensate for breathing or swallowing movement, an important feature in HNC, e.g., when treating glottic laryngeal cancer (75, 76). However, online motion management is not the only solution for such issues: Regarding motion-depended planning- and dosimetry uncertainties, offline-adaptation in different breathing/swallowing positions and calculation of the dosimetric impact might be an additional solution in these cases. Furthermore, exception gating could be applied in order to stop treatment in case of excessive motion (e.g., caused by coughing).

There still exist hurdles and handicaps in treatment planning and delivery, prohibiting a wider clinical use of MRgRT for HNC, with the most important ones being the lack of dynamic IMRT-approaches such as VMAT or dynamic MLC and the increased treatment delivery time with a potential higher treatment burden for the patient. Yet, technical advances are expected to solve these issues in the near future, making this innovative technique available for most HNC-patients. Until then, careful patient selection is of major importance. Patients with advanced tumors or nodal involvement, bilateral neck irradiation, target in proximity to sensible OARs and moving volumes are the most eager to benefit from MRgRT. Mathematical models to predict clinical benefit and guide slot allocation could facilitate patient selection, similar to the ones developed for proton treatment (77–79). Nevertheless, inter- and intra-fractional changes in head and neck tumors and anatomy do not usually take place as quick as, e.g., in the moving organs of the upper abdomen and as most of the times only conventional or slightly hypofractionated regimens are used, the potential additional benefits of online- over offline-adaptation should be always weighted against an extension of treatment time and compromise of the patient comfort. Until less time-consuming and more comfortable procedures are established, the decision regarding the time-point and frequency of plan adaptation has to be critically discussed, also considering the real clinical benefit. An, e.g., only weekly adaptation could be sufficient for many HN patients. In this case, the images could of course be directly acquired on the MR-Linac. Sufficient quality of these images and an MR-only planning procedure would simplify the process compared to an "external" MR-simulation with or without additional planning CT. Running and future trials should focus on possible toxicity reduction, but also on patient comfort, always involving patient reported outcomes (PROMs). Establishing novel, standardized patient positioning and immobilization devices or even treatment without masks based on the experience gathered by PROMs, as well as decision trees and standard operating procedures for the need of re-planning could facilitate a broader clinical implementation of MRgRT for head and neck cancer.

While there is still only a small number of prospective trials investigating applications of MRgRT for HNC, this is expected to increase in the next few years. Challenging fields of research could be not only the decrease of toxicity and the patient selection, but also the development of more advanced hardware, e.g., allowing for VMAT, or software, e.g., for monitor unit verification (66). Finally, the possibility to have access to daily, repetitive imaging during the whole course of radiotherapy could open completely new dimensions with respect to both functional imaging, like diffusion-weighted-MRI (80, 81), and radiomics (82) for predicting tumor response and normal tissue toxicity. This aspect becomes even more interesting through the possibility of comparison of high- (1.5 T) and low-field (0.35 T) magnetic resonance imaging provided by the different platforms.

This study has several limitations, most of all the non-systematic character of the review. Nevertheless, it is the first attempt to summarize the current stand of knowledge regarding MRgRT for the specific and challenging indication of head and neck cancer.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

PB designed the manuscript structure and supervised the content. SB, DM, and JT devised additional ideas, provided images, and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Review of MR-Guided Radiotherapy for Esophageal Cancer

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In this review, we outline the potential benefits and the future role of MRI and MR-guided radiotherapy (MRgRT) in the management of esophageal cancer. Although not currently used in most clinical practice settings, MRI is a useful non-invasive imaging modality that provides excellent soft tissue contrast and the ability to visualize cancer physiology. Chemoradiation therapy with or without surgery is essential for the management of locally advanced esophageal cancer. MRI can help stage esophageal cancer, delineate the gross tumor volume (GTV), and assess the response to chemoradiotherapy. Integrated MRgRT systems can help overcome the challenge of esophageal motion due to respiratory motion by using real-time imaging and tumor tracking with respiratory gating. With daily on-table MRI, shifts in tumor position and tumor regression can be taken into account for online-adaptation. The combination of accurate GTV visualization, respiratory gating, and online adaptive planning, allows for tighter treatment volumes and improved sparing of the surrounding normal organs. This could lead to a reduction in radiotherapy induced cardiac toxicity, pneumonitis and post-operative complications. Tumor physiology as seen on diffusion weighted imaging or dynamic contrast enhancement can help individualize treatments based on the response to chemoradiotherapy. Patients with a complete response on MRI can be considered for organ preservation while patients with no response can be offered an earlier resection. In patients with a partial response to chemoradiotherapy, areas of residual cancer can be targeted for dose escalation. The tighter and more accurate targeting enabled with MRgRT may enable hypofractionated treatment schedules.

Keywords: MRI, esophageal cancer, adaptive radiotherapy, respiratory motion, cardiac toxicity

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INTRODUCTION

Esophageal cancer is the seventh most common type of cancer worldwide with the sixth most common cause of cancer-related death (1). Currently, neoadjuvant chemoradiotherapy (nCRT) followed by an esophagectomy is standard of care for patients with locally advanced resectable esophageal carcinoma (2, 3). Definitive chemoradiotherapy is the preferred approach for unresectable locally advanced esophageal cancer or for patients who decline or are unfit for surgery (4, 5). Thus, radiotherapy plays an important role in the treatment of esophageal cancer. Although nCRT results in an increase in R0 resection rate, locoregional control and improved

overall survival, 5-year overall survival remains poor after trimodality treatment. Moreover, after definitive CRT, disease persistence and locoregional recurrence are common modes of treatment failure, especially in the primary tumor region (6, 7). These poor outcomes warrant improvements in radiotherapy for esophageal cancer patients. This article will provide an overview of the potential benefit and future role of MRI and MR-guided radiotherapy (MRgRT) in esophageal carcinoma.

THE ROLE OF MRI IN ESOPHAGEAL CANCER

Staging

Endoscopic ultrasound (EUS), computed tomography (CT), and positron emission tomography (PET) are typically used for initial staging of esophageal cancer (8). However, all these imaging techniques have limitations with regard to accurate staging, precise tumor delineation for radiotherapy and accurate response assessment after CRT. MRI is a non-invasive technique that provides excellent soft tissue contrast and allows for imaging of cancer physiology. Using T2-weighted (T2W) and diffusion-weighted imaging (DWI), stage T1 tumors can be detected in 33% of cases, T2 in 58%, T3 in 96% and T4 in 100%. MRI has a sensitivity of 38-62% and specificity of 68-85% for N-staging, making it a useful alternative especially in cases where the endoscope cannot pass an obstructing tumor (9). While MRI has had limited historical utilization in esophageal cancer, advances in MRI technology, including faster pulse sequences, cardiac and respiratory gating and surface coils, have improved the resolution of MRIs (10, 11). As these techniques continue to advance it promises greater use of MRI staging for esophageal cancer.

Delineation

Accurate tumor delineation is essential to ensure adequate target coverage while limiting dose to surrounding organs at risk (OARs). Accurate gross tumor volume (GTV) delineation is especially important when cone down or boost strategies are applied. Delineation of the GTV of locally advanced esophageal carcinoma is usually based on CT, FDG-PET, endoscopy, and EUS. Despite this multimodality approach for tumor delineation, the interobserver variability remains substantial, especially in cranial caudal direction (12). The excellent soft tissue contrast of MRI could potentially increase the accuracy of GTV delineation. The GTV appears smaller on breath hold T2W and DWI compared to conventional PET-CT which is acquired during free-breathing. Moreover, the addition of DWI to T2w MRI reduced the variability of the caudal border in tumors involving the GE-junction, showing the potential value of DWI in these cases (12). In a study of 42 patients with esophageal squamous cell carcinoma who underwent breath hold CT and DWI MRI followed by an esophagectomy, the difference in tumor length between CT and pathology was 3.6 mm while the difference in length between DWI and pathology was as low as 0.5 mm (13). Despite the excellent soft tissue contrast provided by MRI a recent study showed that MRI based target delineation did not lead to reduced interobserver variability (12). This might be due to the limited observer experience to date with contouring esophageal tumors on MRI and image acquisition characteristics (axial plane only, slice thickness of 6.5mm).

Response Assessment

After trimodality treatment, approximately one third of patients have a pathological complete response (pCR) (14). Patients who achieve a complete response after nCRT are likely to be unnecessarily exposed to the risks of esophagectomy, with up to 5% mortality, substantial morbidity and a substantial impact on quality of life (14, 15). Unfortunately, current techniques do not reliably identify complete responders (16). If these patients could be accurately identified prior to surgery, surgery might be omitted without jeopardizing outcomes.

Conversely, nearly one fifth of patients have more than 50% vital residual tumor cells in the tumor bed at histopathological examination after nCRT and are considered non-responders. These non-responders are exposed to nCRT related toxicity, probably without benefit. Therefore, accurate identification of non-responders early during the course of nCRT may allow for alternative treatment strategies, such as neoadjuvant treatment intensification, change in chemotherapy, or termination of ineffective neoadjuvant treatment and early surgery.

A meta-analysis of the current literature examining the diagnostic accuracy of clinically routine studies such as endoscopic biopsies, EUS, and PET-CT for detecting residual disease after nCRT showed that single modalities were insufficiently accurate (16). Another meta-analysis on the ability of various imaging modalities for detecting pathological complete response (pCR) showed pooled sensitivities of 0.35, 0.62, 0.01, and 0.80 and pooled specificities of 0.83, 0.73, 0.99, and 0.83 for CT, PET-CT, EUS and MRI respectively (17).

DWI and the derived apparent diffusion coefficient (ADC) and intravoxel incoherent motion (IVIM) models reflect tissue cellular density, extracellular-space tortuosity, and the integrity of cellular membranes (18). Recently, promising results for response prediction have been reported for this functional imaging modality. Baseline DWI prior to CRT therapy, interim DWI midway through treatment, and the change in between baseline and interim imaging have been found to be prognostic and predictive biomarkers (19–24). The relative change in ADC during the first 2 weeks of CRT appears to be the most predictive for residual cancer with a sensitivity of 100% and specificity of 75% (19, 20).

In addition to DWI, dynamic contrast enhanced (DCE) MRI, which involves the serial acquisition of T1-weighted images, before, during, and after the injection of a paramagnetic contrast agent such as gadolinium, provides further insight into the nature of tumor tissue and its close surroundings. DCE imaging reveals characteristics related to tumor vasculature permeability and extravascular extracellular volume (25). DCE imaging can be used to help identify esophageal carcinoma, lymphatic metastases and also predict response to CRT (26–28). Although the performance of DWI and DCE MRI as a single modality are promising, combinations of imaging modalities or

MRI pulse sequences, may provide complementary value and could further improve the prediction of response to CRT (24, 26, 29).

Similarly, the preSANO trial showed that after nCRT, the use of biopsies, FNA, EUS, in combination with PET-CT could identify 70-90% of patients with more than 10% residual carcinoma in the esophagectomy specimen (30). More recently, the prospective PRIDE study aims at the development of a multimodal prediction model including MRI that not only predicts the patients' individual probability of a pCR after nCRT, but also identifies non-responders and patients who are likely to develop distant metastases in the near future (31). Both the SANO and ESOSTRATE trials are comparing active surveillance with immediate surgery in esophageal cancer patients who have achieved a clinical complete response, predicted by PET-CT and endoscopic biopsies, after nCRT (32, 33).

RATIONAL FOR MR-GUIDED RADIOTHERAPY IN ESOPHAGEAL CANCER

Integrated MRI-linear accelerator systems (MR-linacs) provide the ability to adapt the treatment based on daily changes in shape, size and position of the tumor and surrounding tissue in order to increase the accuracy of treatment delivery (19, 20). Due to the enhanced soft-tissue contrast, online MRI will allow real-time tumor visualization both before and during beam delivery. In combination with advanced online motion-compensation, MRgRT could well improve tumor targeting accuracy, allow for smaller planning target volume (PTV) margins and consequently result in a reduction of normal tissue exposure with a potential decrease in treatment related toxicity. Moreover, highly accurate tumor targeting with small PTV margins may enable hypofractionation and less toxic dose escalation to eradicative dose levels, potentially omitting the necessity of surgery to control the macroscopic tumor. Daily and even intrafraction plan adaptation and dose painting based on anatomical changes, tumor regression and functional MR imaging will further refine dose escalation and might provide an organ-sparing treatment strategy for a growing number of patients. The potential advantages of MRgRT for esophageal cancer will be discussed below.

Online Interfraction Tumor Shape Adaptation

The primary tumor, involved nodes and the clinical target volume (CTV) consisting of the peri-esophageal fat often can hardly be discriminated on CBCT. This is particularly true for tumors located in the distal esophagus subject to respiratory and cardiac motion. This is the most common tumor location in the Western world, and often involves the proximal part of the stomach. Hence, set-up corrections are typically performed by online registration of the bony anatomy visible on CBCT, instead of direct matching on the tumor. The interfractional variation of the tumor position and shape in relation to the bony anatomy can be substantial and consequently large PTV margins are required to encompass esophageal tumor (34). Online high-quality MRI facilitates online tumor matching, reducing CTV to PTV margins. A recent study has demonstrated that a 10 mm PTV margin can provide CTV coverage in 89% of cases where daily set up position is based on a bone match (35). Only a modest improvement in CTV coverage to 93% could be achieved with a soft tissue, MRI-guided, CTV match with the same 10 mm margin. This reflects the considerable day-to-day CTV shape changes, especially for distal esophagus and gastroesophageal junction (GEJ), which regularly occurred over the course of treatment and could not be corrected by translational shifts based on soft-tissue registration. This partly explains the modest improvement of geometric coverage of the CTV with online MR-guided soft tissue matching and indicates that correction for the largest interfraction positional variation can only be achieved by daily online adaptation of the target and online replanning (35).

In addition to positional variation of GTV and CTV, substantial tumor volume regression during the course of nCRT can be visualized on MRI. By the fifth week of treatment, esophageal tumors can decrease by 28% of the initial volume (36). This tumor regression will predominantly result in deformation of the target and, as a consequence, OARs, especially the heart, could move into the initial GTV, thereby increasing the radiation dose to the heart and contributing to cardiac toxicity (**Figure 1**). The effect of tumor regression on the anatomical configuration can only be appreciated with online MR-guidance and corrected for by an online adaptive workflow where a new treatment plan is generated based on the anatomy of the day. This procedure, also referred to as adapt-to-shape (35) or stereotactic MR-guided adaptive radiation therapy (SMART) (37), will correct for interfraction variation.

Dealing With Intrafraction Tumor Motion

Intrafraction motion due to respiratory motion revealed by cine MRI average 12–13 mm in the cranial-caudal (CC) direction, 2.5–5 mm in the anterior-posterior (AP) direction, and 2.7 mm in the left-right (LR) direction (38, 39). Lower esophageal tumors and GEJ tumors exhibit the largest motion and variability of motion during the respiratory cycle due to their proximity to the diaphragm (34, 40). In general, respiratory motion of esophageal tumors will cause a decrease in the sharpness of the dose gradient at the PTV edge, predominantly in CC direction, once the position of the target volume has been properly identified (41). Although the intrafraction motion of esophageal tumors can be categorized as modest and seldom leads to systematic errors, motion management techniques (e.g. respiratory gating, or mid-position techniques) are required to bring down CTV-to-PTV margins to 2–3 mm-levels in future treatments. Moreover, drift during treatment can be observed and although in general drifts are small with a mean of 1.5 mm, outliers up to 11 mm can occur (39).

MRgRT allows for online tumor motion monitoring, which affords the option to intervene in case of extreme anatomical changes and drifts are observed. Moreover, respiratory gating

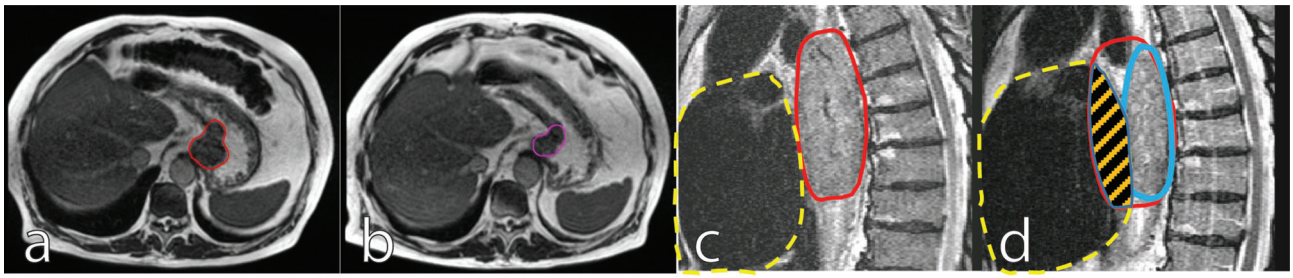

FIGURE 1 | Mid treatment gastroesophageal adenocarcinoma tumor regression: Images are inhale breath hold 0.35T True Fast Imaging with Steady-State Free Precession (TRUFI) at baseline [**(A)**, red outline] and on fraction 10 of chemoradiation therapy [**(B)**, purple outline]. Sagittal views of thoracic squamous cell carcinoma tumor regression depicted 1.5T T2-weighted navigation triggered imaging at baseline [**(C)**, red outline] and on fraction 19 of chemoradiotherapy [**(D)**, blue outline]. In **(C, D)**, the dashed yellow shows the heart contour and the striped orange area shows regression from the overlap of the original tumor volume and the heart volume.

can mitigate the effect of respiratory motion and reduce the required PTV (42). On conventional linear accelerators, respiratory gating is performed using external surrogates, but the correlation between such surrogates and tumor motion can vary substantially (43). As such, image guidance is of utmost importance for accurate respiratory gating to avoid a geographical miss. MRI allows real-time position confirmation during gated treatment by tracking the GTV, ensuring accuracy of the treatment.

Reducing Treatment-Related Toxicity

Smaller CTV to PTV margins will result in less dose to the surrounding organs at risk and thereby will theoretically decrease treatment related toxicity. In patients undergoing CRT for esophageal cancer, up to 10.8% develop symptomatic cardiac toxicity (44). Institutional retrospective and database analyses show that compared to patients who undergo esophagectomy alone, those who undergo nCRT have a significantly increased risk of grade 3 or higher cardiac events and that higher radiation doses to the heart correlates with a higher incidence of cardiac events (45–47). In a prospective phase II trial by Lin et al, 145 patients with esophageal cancer were randomized to definitive treatment with proton beam therapy or photon-based intensity-modulated radiation therapy. At a median follow up of 44 months, the total toxicity burden was lower in the proton beam therapy arm, with pronounced numeric differences in cases of atrial fibrillation, asymptomatic effusions, lower-grade pneumonitis, acute respiratory distress syndrome (ARDS) and reintubation. This study demonstrated that the dosimetric advantages of proton therapy resulted in lower rates of toxicity (48). Similar benefits could be expected from daily online adaptive MR-guided radiotherapy plans with tight CTV to PTV margins. MRL treatments using maximum inspiration breath hold under real time MRI tracking can help reduce treatment volumes. In a dosimetric analysis, compared to free breathing treatments on conventional CBCT guided radiotherapy, maximum inspiration breath hold MRL treatments for GEJ tumors can reduce the PTV from 1275 cc to 689 cc with a corresponding decrease in mean heart dose from 27.8 Gy to 20.9 Gy (42). While photon-based MRL treatments may have larger volumes of low dose coverage of OARs, due to uncertainties of the location of the Bragg peak, proton-based treatments are likely to have larger volumes of high dose coverage of proximal OARs. Future studies are warranted to compare the toxicity burdens between photon-based MRL treatments and proton therapy. The ability to visualize moving soft-tissue tumors with MRI and the dosimetric advantages of the Bragg peak with proton therapy could be combined in a hybrid system for MR-integrated proton therapy (MRiPT). Although MRiPT is still in its infancy, research is currently underway to develop prototype systems for clinical use (49). In addition to MR-guided daily plan adaptation and PTV margin reduction with consequently better sparing of OARs, MRI may also provide a way to detect subclinical cardiac toxicity after CRT by visualizing areas of myocardial fibrosis and changes in ejection fraction (50).

Besides limiting the radiation dose to the heart, smaller margins with MRgRT can also reduce the dose to the lungs and stomach. Grade 2 or higher radiation pneumonitis affects 5-7% of patients undergoing intensity-modulated radiotherapy for esophageal cancer, with greater incidence seen at higher lung V20 doses (51). Recent studies indicate that the ratio of the planning target volume to the total lung volume and the mean lung dose are important for predicting the probability of developing severe acute radiation pneumonitis (52). In patients who undergo esophagectomy, anastomotic leak rates range from 0–24% and are the cause of 90% of postoperative mortalities (53). The relationship between nCRT and rates of anastomotic leaks is controversial. The odds ratio for developing an anastomotic leak is 5.37 within the radiation field compared to anastomoses outside the radiation field (54, 55). However in studies comparing patients treated with neoadjuvant radiation therapy to resection alone, there was no difference in anastomotic leak rates (56, 57). Target definition at the GEJ is challenging and daily variation in this area can be substantial, therefore accurate dose accumulation in the area will be difficult, which might explain the conflicting results.

TARGETED DOSE ESCALATION

Although progress has been made in the treatment of esophageal cancer, treatment still fails in most patients due to locoregional

recurrences and the development of metastatic disease. The majority of local recurrences after definitive chemoradiation occurs within the GTV, suggesting a potential benefit of dose escalation in patients unfit for surgery or with unresectable disease (6, 7). Furthermore, the generally applied tumor radiation dose of 41.4 to 50.4 Gy is far below the commonly used doses at other primary tumor sites, such as lung and head and neck tumors. Patients treated with nCRT might benefit from dose escalation by increasing the chance of achieving a pCR. Moreover, patients with a pCR have a favorable prognosis (58) and it could be argued that surgery might be safely omitted in these patients.

Currently, results of dose escalation studies are inconsistent. A landmark randomized trial INT-0123 (RTOG 94-05) revealed that sequential dose escalation to 64.8 Gy did not translate into an increase in local control or overall survival in esophageal cancer. Radiotherapy techniques have evolved dramatically since the era of the INT-0123 trial and several retrospective and non-randomized prospective studies have shown an increase in local control after dose escalation (59–61). The ARTDECO trial, published in abstract form in 2020, randomized inoperable esophageal cancer patients (61% squamous cell carcinoma and 39% adenocarcinoma) to conventional CRT with a simultaneous integrated boost to a total of 61.6 Gy. Although modern radiation techniques were used, local progression free survival and overall survival were not statistically different between the two groups while the dose escalated arm had higher rates of grade 4-5 toxicity (62). The location and histology of the tumor may influence outcomes of dose escalation studies. Lower esophageal tumors are more challenging to treat. They tend to be adenocarcinoma which are more radioresistant than squamous cell carcinoma, have more cardiac and respiratory motion due to proximity to the heart and diaphragm, are pressed tightly to the adjacent heart, and are limited by proximity and radiosensitivity of the stomach.

The inconsistent results of dose escalation regarding local control and overall survival might also be due to the lack of patient selection. Careful selection of patients for a sequential boost based on the initial PET-CT response to standard CRT showed promising results (63).

FUTURE PROSPECTS OF MRI AND MR-GUIDED RADIOTHERAPY IN ESOPHAGEAL CANCER

Currently, at the UMC Utrecht the first patients with esophageal cancer are being treated on the 1.5T MR-Linac with reduced margins. Patients receive standard fractionated nCRT with reduced PTV margins (**Supplementary Materials**, **Figure S1**). This combined R-Ideal phase 1b-2a study with smaller PTV margins will serve as a proof of concept and the workflow and technology will be further optimized for future innovative treatments, such as dose escalation (64).

MR guided radiotherapy provides an exciting opportunity to improve and personalize esophageal cancer treatment by various means. First, MRI appears to be promising in treatment response assessment to guide patient-tailored treatment strategies, such as dose escalation or organ preservation. Second, online MR guided radiotherapy will result in high precision daily adaptive radiotherapy with reduced margins, thereby reducing toxicity and enabling safe targeted dose escalation. Finally, functional MR-guidance allows for dose painting strategies based on biological information about the tumor in order to increase its efficacy, such as dose escalation to only the parts of the GTV that exhibit persistent tumor activity at the end of standard CRT (**Figure 2**) (65). Randomized trials are needed to demonstrate the effectiveness of MR-guided radiotherapy compared to conventional CBCT guided radiotherapy.

In addition, the increased accuracy of online MR guided radiotherapy, due to daily adaptation of target delineation and online replanning in combination with beam on imaging, might pave the way for hypofractionated dose escalation in esophageal cancer. Hypofractionated radiotherapy has the advantage of a shorter overall treatment time and a higher biological

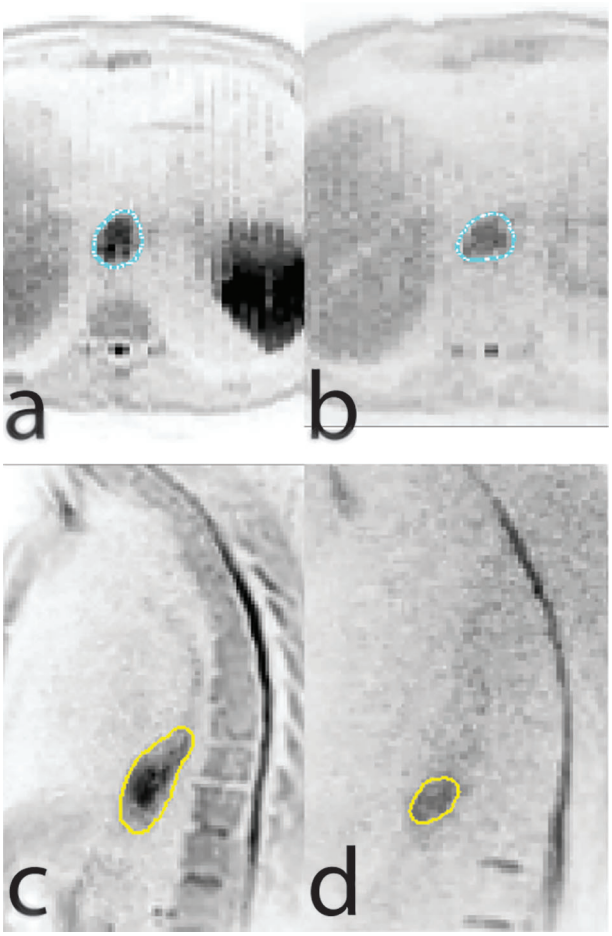

FIGURE 2 | Axial **(A, B)** and sagittal **(C, D)** views of a diffusion weighted imaging scan conducted at baseline **(A, C)** and at week five of chemoradiation therapy **(B, D)** showing regression of tumor size but persistent diffusion restriction.

effectiveness. Future studies need to elucidate whether hypofractionated radiotherapy will improve outcomes in esophageal cancer in terms of local control, will lead to adequate functional outcomes and is safe in terms of esophageal toxicity.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

SL, MB, and SM were responsible for the conception of this review. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.628009/full#supplementary-material

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PERSPECTIVE
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MR-Guided Radiotherapy for Rectal Cancer: Current Perspective on Organ Preservation

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Online MRI-guided radiotherapy (MRgRT) is one of the most recent technological advances in radiotherapy. MRgRT permits the visualization of tumorous and healthy tissue while the patient is on the treatment table and online daily plan adaptations following the observed anatomical changes. In the context of rectal cancer, online MRgRT is a very promising modality due to the pronounced geographical variability of tumor tissues and the surrounding healthy tissues. This current paper will discuss the possible applications of online MRgRT, in particular, in terms of radiotherapy dose escalation and response prediction in organ preservation approaches for rectal cancer.

Keywords: radiotherapy, rectal cancer, MRI, MR-linac, dose escalation

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INTRODUCTION

Neoadjuvant (chemo)radiotherapy (NCRT) represents the reference standard in the treatment of locally advanced rectal cancer (LARC), primarily aiming to reduce local recurrence rates after surgery (1). MRI with its superior soft-tissue contrast has gained a crucial role in the initial staging and response assessment of rectal cancer and can stratify patients into different prognostic groups with risk-adjusted personalized therapeutic approaches (2, 3).

A promising driver of precision RT in rectal cancer is the recent introduction of linear accelerators with an onboard MR scanner, the MR-Linac. This new treatment machine enables online MRI-guided RT (MRgRT) which opens a new era for an image-guided and online adaptive RT (4). At the time of writing, two commercial 35 solutions are available for clinical use: the MRIdian system by ViewRay (ViewRay Inc, USA), which was first released in 2014 coupling a low tesla scanner (0.35 T) with a triplet of ^{60}Co heads and was later replaced by a 6 MV linac, and the Unity system by Elekta (Elekta AB, Sweden), which uses a 1.5 T scanner and a 7 MV linac, released in 2017 (5–7). Despite the low number of active hybrid units, there is a growing interest on the role of this advanced irradiation technique (4, 8).

One of the areas of interest and current research on rectal cancer is the organ preservation approach (9). With the current therapeutic approaches, pathological complete response (pCR) after NCRT for LARC is in the range of 10–20% in most trials. There has been a great interest in developing strategies with tolerable toxicity to increase the number of patients who achieve a complete clinical response and, therefore, could be managed in a non-operative manner in the framework of a "watch and wait" approach (10, 11). These strategies include the intensification of

systemic treatment, the prolongation of the interval between neoadjuvant therapies and response assessment or surgery, total neoadjuvant therapy, hyperthermia, and radiotherapy dose escalation (12–16). The latter strategy has been hampered so far by the very limited resolution of cone-beam CT (CBCT)-based images, resulting in large safety margins. Furthermore, response prediction is a field with a need for tailored treatment approaches.

This review aims to present and discuss opportunities with online MRgRT in the treatment of rectal cancer.

ADAPTATIONS FOR THE CHANGING ANATOMY

Variations in the target position during radiotherapy for rectal cancer are largely due to daily changes in bladder and bowel filling. For the elective target volumes used to treat patients in the neoadjuvant setting, the position variations are most prominent in the mesorectum, specifically in the anterior part of the upper mesorectum, where the position of the mesorectum is dependent on both rectal and bladder filling, and with deformations of up to 7 mm (17–19). Besides interfraction variations due to changes in the filling of the organs in the pelvis, there is also a possibility of tumor regression during the treatment course, which changes the anatomy. On average, rectal tumors can reduce almost 50% in volume during the treatment course (20, 21). These variations are, in most cases, not relevant in the neoadjuvant setting as the gross target volume (GTV) is inside the mesorectum in most cases but becomes very relevant in the setting of dose escalation. Taking into account these uncertainties at the target position, generally large clinical target volume (CTV) to planning target volume (PTV) margins are used around the target volumes of up to even 2.3 cm, which leads to a considerable burden on the healthy tissues (18, 19). Different adaptive strategies have been proposed to reduce the need for large margins in the neoadjuvant treatment setting. One of the most promising techniques is the library of plans (LOP) strategy (22). In this strategy, the CTV from a single planning CT is contracted and expanded based on population variation statistics, and multiple radiation treatment plans are generated based on different CTVs. For each fraction, the plan is chosen with the CTV that best matches the actual volume as visualized on the localization CBCT. Applying the LOP strategy allows reductions of, on average, 15% in the PTV compared to conventional treatment, but the daily selection of the appropriate plan can be challenging due to poor CBCT image quality (20, 21). Furthermore, while this approach is useful for an adequate coverage of the mesorectum, it is no longer a reliable tool for dose escalation of the tumor itself. With MRgRT, it is possible to adapt daily treatment plans based on MRI-visualized anatomy. The superior soft-tissue contrast of MRI compared to CBCT gives the opportunity to not only see the mesorectum and organs at risk but also to visualize the primary tumor and pathological lymph nodes during each fraction. **Figure 1** shows representative scans from the 0.35 T and 1.5 T MR-Linac. Based on this daily visualized anatomy, different adaptive treatment strategies can be chosen from a simple translation of the treatment fields to full online replanning (7). The radiotherapy dose escalation strategy takes around 50 min for each treatment fraction and allows the use of smaller CTV to PTV margins of 4–6 mm (23). Reduced margins and daily adaptation of treatment fields lead to a reduced spread of the dose in the surrounding healthy structures, such as the surrounding uninvolved rectal wall, the small bowel, the bladder, and the anal sphincter, potentially resulting in less radiotherapy-related short- and long-time side effects. This is particularly important for the expanding group of patients who are treated with watchful waiting strategies, as, for these patients, a treatment with limited toxicity and a satisfactory anorectal function after (chemo)radiotherapy is of utmost importance (24).

DOSE ESCALATION

In order to increase the number of patients eligible for organ preservation strategies, innovative and novel treatment protocols to maximize complete response rates are needed. This can be achieved by increasing the radiotherapy dose to the primary tumor as shown in the dose-response curve presented by Appelt et al. (25). This dose-response curve was constructed based on studies that delivered a brachytherapy boost after external beam radiotherapy for locally advanced rectal cancer. Moreover, a systemic review by Burbach et al. showed a potential effect of external beam radiotherapy dose escalation. At the same time, two recent prospective randomized trials did show an increased tumor response with external beam dose escalation, but not in terms of pathological complete response or sustained clinical complete response (26, 27). An explanation for these negative results can at least partly be seen in the limitations of CBCT-based dose escalation, in particular, limited target coverage. Large safety margins had to be used because of the aforementioned poor target, and organ-at-risk visibility with CBCT imaging and organ-at-risk constraints resulted in reduced coverage of the tumor in many cases (28). Another aspect in both the clinical trials was the high complete rate observed in the standard arm underlining the critical need for parameters that identify patients who are unlikely to benefit from dose escalation since they already have a very favorable phenotype. More precise delivery of the external beam irradiation with online MR guidance dose can probably solve the issue of target volume coverage as tumors can be visualized with MRI immediately before and during dose delivery. This solution has a clear advantage of online adaptive MRgRT over "offline" adaptive strategies with pre-defined time points for adaptation (29). Besides, by daily online replanning, the margins needed can be minimized and treatment volumes for dose escalation will be smaller, potentially facilitating dose escalation beyond the biologically effective dose of ∼65–70 Gy used in the recently published dose escalation studies (26, 27). This is supported by a recent radiotherapy planning study by Bonomo et al. based on sequential MRI scans, showing that an online adaptive boost strategy results in lower doses to the rectum and the anal canal (30). MR-guided dose escalation strategies are currently under development, and the organ preservation potential of these new schemes will be tested in innovative trials. While the safety of extreme dose escalation under MRI guidance

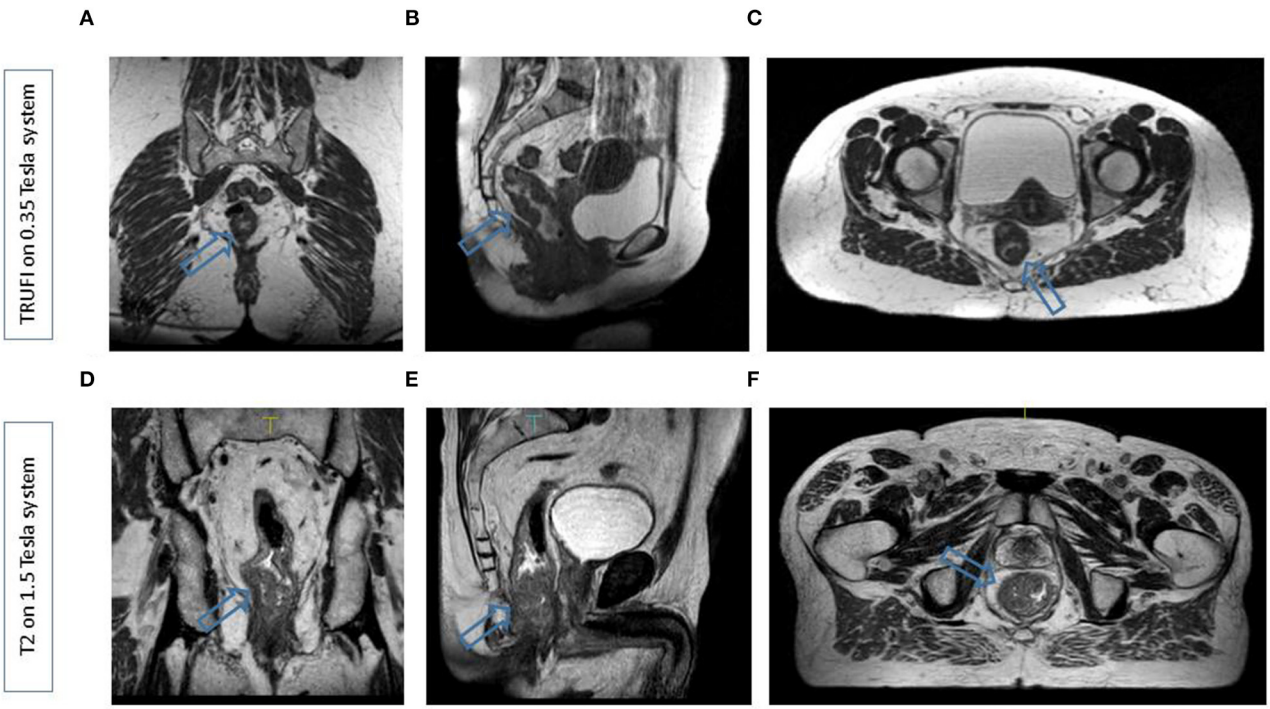

FIGURE 1 | Representative scans from the 0.35 T MR LINAC **(A–C)** in the coronal, sagittal, and transverse planes and the 1.5 T MR LINAC **(D–F)** in the coronal, sagittal, and transverse planes. In both cases, a patient with a distally located rectal tumur was scanned. Arrows indicate the tumur.

needs clinical proving, the experience in prostate cancer suggests that the rectum can tolerate a high dose localized to a small volume (31). MR-guided dose escalation may also help facilitate an R0 resection in challenging surgical cases. Rectal tumors with threatened mesorectal margins, pelvic sidewall invasion, or iliac lymph node involvement are at high risk for incurable local recurrences. Radiation boost can be used to decrease the risk of positive surgical margin in these cases or to eradicate tumor cells in lymph nodes that are not routinely resected.

FUTURE PERSPECTIVES: PRECISION RT WITH THE INCLUSION OF PREDICTION MODELS AND FUNCTIONAL IMAGING

Besides the intuitive approach of using anatomical MR sequences for the adaption of treatment plans following the anatomy of the day, there has been a great interest in using functional imaging data and advanced image analysis for precision radiotherapy of rectal cancer (32, 33). Data from the literature supports various hypotheses on how diffusion-weighted imaging in particular might be a very useful tool. First, it has been shown that early changes in the apparent diffusion coefficient (ADC) can predict response to radiochemotherapy more accurately than early changes in tumor volume (34). Interestingly, the predictive value of early changes in ADC, for instance from baseline to week two of treatment, was superior to baseline ADC values, likely reflecting biological properties of the tumor. As described earlier, adequate patient selection is a key component of dose escalation strategies. A considerable number of patients can achieve a complete response without dose escalation and will have no benefit from dose escalation. Therefore, selecting patients for dose escalation based on changes in functional imaging data is a very interesting approach. With MR-linac hybrid devices, it is possible to acquire these data "in one go," while the patient is on the table and being treated. Moving one step beyond, one could also envision defining tumor subvolumes that have a high likelihood of harboring residual tumor cells and use these volumes for dose-escalated treatment as supported by a study by Shaverdian et al. (35). Furthermore, the large amount of imaging data that is acquired during the course of the treatment can be used to generate, optimize, and validate prediction models in the context of quantitative imaging data and radiomic analysis (36, 37).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors were involved in the writing of this perspective paper. CG and LB provided the figure.

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REVIEW
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MR-Guided Radiotherapy for Liver Malignancies

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MR guided radiotherapy represents one of the most promising recent technological innovations in the field. The possibility to better visualize therapy volumes, coupled with the innovative online adaptive radiotherapy and motion management approaches, paves the way to more efficient treatment delivery and may be translated in better clinical outcomes both in terms of response and reduced toxicity. The aim of this review is to present the existing evidence about MRgRT applications for liver malignancies, discussing the potential clinical advantages and the current pitfalls of this new technology.

Keywords: magnetic resonance guided radiotherapy, stereotactic body radiation therapy, image guided radiation therapy, liver malignancies, liver cancer, online adaptive radiation therapy

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INTRODUCTION

The recent introduction of integrated magnetic resonance (MR) linear accelerators (linacs) into clinical practice has opened new perspectives for radiation therapy (RT), offering the advantages of coupling 0.35 or 1.5 T on-board MR scanners firstly with a triplet of ^{60}Co heads and later with 6 and 7 MV linacs in stand-alone hybrid units (1–3). MR guided radiotherapy (MRgRT) has been successfully applied to several anatomical sites, exploiting online adaptive planning solutions and innovative motion management, with improved dosimetric performance and early clinical results suggesting improved efficacy and toxicity reduction (4–6). Despite the numerous explored applications, the published clinical evidence is still scarce, and the actual quantification of the

Abbreviations: ADC, Apparent diffusion coefficient; ART, Adaptive radiotherapy; ATP, Adapt-to-position; ATS, Adapt-to-shape; BCLC, Barcelona Clinic Liver Cancer; CBCT, Cone beam computed tomography; CBD, Common bile duct; CRC, Colorectal cancer; CT, Computed tomography; DCE, Dynamic contrast enhanced; DEB-TACE, Drug-eluting bead transarterial chemoembolization; DIBH, Deep inspiration breath hold; DNN, Deep neural networks; DP, Delayed phase; DVH, Dose-volume histogram; DWI, Diffusion weighted imaging; FFLP, Freedom from local progression; HBP, Hepatobiliary phase; HCC, Hepatocellular carcinoma; IBT, Interstitial brachytherapy; IGRT, Image guided radiation therapy; ITV, Internal target volume; IVIM, Intravoxel incoherent motion; kV, Kilo-voltage; LC, local control; LPFS, local progression free survival; MLL, metastatic liver lesions; MR, Magnetic resonance; MRgART, MRI-guided online adaptive radiotherapy; MRgRT, Magnetic resonance guided radiotherapy; MRI, Magnetic resonance imaging; MWA, Microwave ablation; NETs, Neuroendocrine tumors; OAR, Organ at risk; OS, Overall survival; PEI, Percutaneous ethanol injection; PRV, Planning organ at risk volume; PVP, Portal venous phase; PVTT, Portal vein tumor thrombosis; PTV, Planning target volume; RFA, Radiofrequency ablation; RILD, Radiation-induced liver disease; RT, Radiation therapy; SBRT, Stereotactic body radiation therapy; SMART, Stereotactic MR-guided adaptive radiation therapy; T1WI, T1 weighted image; T2WI, T2 weighted image; TACE, Transarterial chemoembolization; TPS, Treatment planning system; TRUFI, True fast imaging.

advantages of using such an advanced technology is still the object of debate in the radiation oncology community (7). The types of cancers generally considered most suitable for MRgRT are those located in anatomical sites where similar levels of tissue density in computed tomography (CT) imaging do not allow a precise identification of the different therapy volumes, especially if they are movable and particularly close to radiosensitive organs at risk (OAR).

In this framework, liver malignancies appear to be ideal for MRgRT applications for several reasons, especially when considering the growing role that stereotactic body radiation therapy (SBRT) is gaining in the treatment of both primary liver tumors or liver metastases (8–10). MRgRT could indeed be a competitive option to improve tumor control, especially during hypofractionated radiotherapy and for tumors that are poorly visualized on standard radiotherapy CT imaging (*i.e.* liver cancers). Furthermore, the innovative online adaptive solutions have made it possible to dose escalate to ablative doses even for targets close to sensitive OARs (*e.g.* bowel loops, duodenum, stomach) (4, 8, 11–13).

The aim of this article is to describe the state of the art of MRgRT for liver tumors, focusing on the most promising liver cancer clinical indications, the role of the different MRI sequences provided by the hybrid scanners, and the advantages of applying motion management and advanced adaptive approaches using MRgRT.

LIVER MRgRT CLINICAL INDICATIONS

The role of RT in the management of primary and secondary liver tumors has substantially increased over the years. Emerging data suggest local treatment benefit for both hepatocellular carcinoma (HCC) and oligometastatic disease, integrating radiation therapy (RT) in different ways with available systemic and local therapies (14). In both the aforementioned disease conditions, the treatment of choice is surgery with 5-years survival rates of 30–60% for colorectal cancer (CRC) liver metastases and 50% for HCC, with 4-years survival of 74% after liver transplantation (15–17). Other liver-directed treatments, such as radiofrequency ablation (RFA), interstitial brachytherapy (IBT), microwave ablation (MWA), or percutaneous ethanol injection (PEI) are valid treatment options for small tumors when surgery is not possible, *e.g.* due to comorbidities or limited liver reserve (17). Transarterial chemoembolization (TACE), Yttrium-90 (^{90}Y) transarterial radioembolization, and drug-eluting bead transarterial chemoembolization (DEB-TACE) are regional, non-curative therapies used to improve survival in selected HCC patients (18, 19). Many patients with liver cancers are not well suited for these local–regional therapies, and many others develop recurrences despite the use of these therapies. Thus there is a potential role for RT to be used to treat these patients who may not be treated with ablative therapies otherwise. Liver radiotherapy has been historically used for palliation, but its therapeutic paradigm is changing, in part due to the application of SBRT which allows a high conformation of the dose to the target with efficacious sparing of the OARs and significant reduction of the risk of radiation-induced liver disease (RILD), which represents an important cause of comorbidity, especially for primary liver cancers (20).

Primary Liver Lesions

Numerous trials have demonstrated the effectiveness of SBRT in primary liver cancers, but there is still no conclusive scientific evidence to definitely determine the role and benefits of RT in this setting (21, 22). SBRT plays a major role mainly when surgery or other local ablative procedures (*e.g.* RFA) are contraindicated or high risk. Such patients may have early stage tumors with a high chance of sustained local control, *e.g.* HCC early stage by the Barcelona Clinic Liver Cancer (BCLC) classification: solitary lesions ≤5 cm in maximum diameter or multiple nodules (≤3 total) measuring ≤3 cm in maximum diameter, absence of vascular invasion and extra hepatic metastasis (23). SBRT can also be used as a salvage treatment after other local therapies have failed (23). Alternatively, SBRT has an increasing role in intermediate and advanced stage tumors, where avoiding toxicity is important.

The feasibility and effectiveness of SBRT have been demonstrated in comparative studies between SBRT and RFA and between SBRT in combination with TACE *versus* SBRT alone, without negative impact on the toxicity profile (24–26). Particular caution should be used for patients with more impaired liver function, *e.g.* Child Pugh score >8 points, reserving SBRT only as a bridge to transplantation, since a correlation with increased liver toxicity has been reported in these patients subset (27–29).

Encouraging results of SBRT on survival and toxicity have also been reported in patients where TACE and surgery are contraindicated due to the presence of portal vein tumor thrombosis (PVTT) (30, 31). Small series have reported results following the combination of SBRT with Sorafenib, a multikinase inhibitor targeting the Raf/MEK/ERK pathway, and caution is suggested in this subset of patients due to the possible increase of hepatic toxicity for possible post irradiation impairment of normal tissue recovery process secondary to anti VEGF activity (32–34).

Immunotherapy, in particular, therapies targeting PD-L1-PD-1 pathways (*i.e.* checkpoint inhibitors, Atezolizumab) and antibodies targeting vascular endothelial growth factor (VEGF), is taking on an emerging role. The combination of atezolizumab and bevacizumab has been shown to result in better OS and PFS outcomes than Sorafenib in patients with unresectable HCC (35).

Lastly, even if not supported by robust evidence, some published experiences also suggest a potential role for SBRT also in the management of cholangiocarcinoma, especially when combined with systemic therapies (36).

Liver Secondary Lesions

SBRT plays an important role also in the management of non-resectable oligometastatic liver disease, and several studies have demonstrated the role and effectiveness of SBRT as a non-invasive, well-tolerated, and promising therapeutic approach,

especially in the light of the aforementioned technological progress represented by MRgRT.

Hypofractionated regimens have been adopted for some time now, showing promising results on local disease control, but the potential for unnecessary high dose OAR irradiation, linked to increased rates of toxicity, has limited widespread use of SBRT (37–40). The optimization of traditional SBRT delivery technologies (*i.e.* Cone beam CT, CBCT, IGRT protocols, and fiducial based irradiation) has achieved better local control rates for small lesions, reporting local control rates >90% when doses of 46–52 Gy are delivered in three fractions for unresectable colorectal metastases (41, 42). Dose escalation appears therefore to be directly linked to local control and clinical outcomes, and MRgRT may ensure higher degrees of safety and efficacy.

Multidisciplinary assessment is recommended to identify patients who may be eligible for SBRT, based on location, size, and morphology of liver lesions and on patient performance status, liver function, and residual healthy liver volume (42). Careful selection of patients for ablative therapies is required when there is a potential risk of RILD or when patients have comorbidities that contraindicate invasive treatments. SBRT can be used for metastatic lesions that are challenging to be treated with RFA due to their proximity to critical structures (*e.g.* subcapsular, periampullary, perihilar or when adjacent to vascular structures). An advantage was shown in terms of 1-year freedom from local progression (FFLP) when SBRT is compared to MWA when larger lesions are treated (43, 44). Furthermore, recent data encourage the use of RFA and SBRT for the management of multiple liver metastases (45).

Clinical MRgRT Liver Evidence

Rosenberg et al. (11) and Feldman et al. (46) have focused on the feasibility of MRgRT in the treatment of both primary and secondary hepatic neoplasms. Rosenberg et al. (11) analyzed the outcomes of 26 patients treated with MRgRT SBRT technique in different institutions. Patients with both Child–Pugh A or early B and presenting one to three liver lesions were included. Median PTV was 98.2 cc (13–2,034), with a median delivered dose of 50 Gy in five fractions, and median liver dose of 12.7 Gy (3.2–21.9). The applied gating protocols were deep inspiration breath hold (DIBH) (16 patients) and modified shallow internal target volume or exhale-based setup for treatment (10 patients), depending on the patient's compliance. At 21 months follow-up, local control rate was 80.4% with grade 3 gastrointestinal toxicity found in two patients (7.7%, with one case of portal hypertension and one of hilar stricture requiring procedures) who had a large treatment volume and had undergone previous liver-directed treatments. The 1-year and 2-years OS were 69 and 60% respectively.

In the cohort of 29 patients treated by Feldman et al. (46), 26 were affected by HCC, two by cholangiocarcinoma, and one presented liver metastases. A total of 31 lesions were treated with a dose ranging from 45 to 50 Gy in five fractions, while the remaining three were treated with doses from 27 to 42 Gy in three fractions. The mean liver dose was 5.56 Gy (1.39–10.43). Motion was managed by treating 21 patients in end-exhale, six in end-inhale, and two in free breathing conditions. One patient was also treated with adaptive technique. Patients were monitored in follow-up from one to 12 months post-treatment, showing either stable or decreased size of all but one treated lesion. The highest observed toxicity was grade G2 with a case of nausea and vomiting and a case of abdominal pain with melena that did not require pharmacological intervention, but only a brief interruption of treatment.

Moreover, Henke et al. (47) reported the potential of the Stereotactic MR-guided adaptive radiation therapy (SMART) approach (48) in a cohort of oligometastatic patients including 11 patients affected by secondary liver lesions and four with HCC. At median follow-up of 15 months only two patients with recurrent locally advanced pancreatic cancer underwent local progression. No grade 3 toxicity has been observed in this cohort of patients, while 6-months local progression free survival rate and 1-year OS were of 89.1 and 75% respectively. Hal et al. (49) recently presented data from a cohort of 10 patients affected by upper abdominal neoplasms (of whom four were affected by secondary liver lesions and two by HCC), treated with 1.5 T MR-linac.

HCC patients received 40–45 Gy in five fractions, while those with metastatic lesions 45–60 Gy in three fractions or 50 Gy in five fractions. A 4DCT and a 4DMRI with IV contrast agent were acquired in the simulation phase.

Motion was managed creating an ITV from the 4DCT simulation. Treatment has been carried out with both adapt-to-position (ATP) and adapt-to-shape (ATS) approaches, and the delivery has been performed with a real-time cine MRI acquired in three perpendicular planes. At 7.2 months follow-up, two patients developed G2 skin toxicity, and no local recurrences or progression of the treated lesions was recorded. The feasibility and patients' acceptability of MRgRT were investigated in a prospective study that enrolled 43 patients, including eight with liver lesions, who underwent respiratory-gated treatments in DIBH, of which 47% SBRT (50). The treatment was carried out with visual guidance of the live sagittal low T cine-MRI during gated delivery coupled with audio feedback when necessary. Patients compiled an in-house developed patient-reported outcome questionnaire to document their treatment experience and tolerance. Although 65% of patients reported some MR-related complaints (*e.g.* paraesthesia, uncomfortable positioning), MRgRT was overall defined as positive or at least tolerable.

All patients reported high levels of satisfaction related to their active participation in treatment. No acute toxicity ≥G2 was recorded in the entire cohort, except for four patients reporting G2 fatigue.

Table 1 summarizes some of the clinical studies on the use of MRgRT in the treatment of hepatic malignancies.

MRI IMAGING CHARACTERIZATION

The reliable identification of liver lesions on hybrid MR imaging depends on several issues and has direct consequences in RT treatment planning (*i.e.* planning target volume, PTV, margin

TABLE 1 | Recent clinical studies on the role of MRgRT in hepatic malignancies.

Reference	year	dose	Patients (n)	Response
Henke et al. (51)	2018	50 Gy in 5 fractions	10 non-liver abdomen lesions 6 MLL 4 HCC	3-months LPFS 95% 6-months LPFS 89.1% 1-year OS 75%
Feldman et al. (46)	2019	45 to 50 Gy/5 fractions	26 HCC 2 cholangiocarcinoma 6 MLL	1 year LC 96.5% 1 year OS 92.8%
Rosenberg et al. (11)	2019	Median dose 50 (30–60) Gy in 5 fractions	6 HCC 20 MLL	1-year OS 69% 2-years OS 60%
Hal et al. (49)	2020	Median dose 45 (25–60) Gy in 3 to 5 fractions	3 Pancreatic cancer 2 HCC 1 pancreatic metastasis 4 MLL	7.2-months LC 100%
Luterstein et al. (52)	2020	Median dose 40 Gy in 5 fractions	17 cholangiocarcinoma	1-year OS 76% 2-year OS 46.1% 1-year LC 85.6% 2-year LC 73.3%.
Boldrini et al. (53)	2021	Median dose of 50 (50–55) Gy in 5 fractions	10 HCC	6,5-months LC 90%
(ClinicalTrials.gov. NCT04242342) (54)	2019–recruiting	50–60 Gy in 5 to 6 fractions	46 Primary or secondary liver tumor(s)	2 years LC Lack of progression according to RECIST criteria

MLL, metastatic liver lesions; OS, overall survival; LC, local control; LPFS, local progression free survival.

definition, and gating solutions). Magnetic resonance scanner field strength, presence of image artefacts (especially respiratory related ones), used sequence, and the administration of contrast agents should be considered among the technical ones. Other clinical and patient's specific parameters have specific consequences on image quality and reliability for radiotherapy segmentation and planning purposes, such as the kind of disease (primary liver tumors or secondary lesions), the involved hepatic segment or specific anatomical conditions. MR-linacs currently allow the acquisition of a default sequence which is similar to the standard "true-FISP", both in the 0.35 and 1.5 T clinical solutions. This sequence generally allows tumor identification and easier segmentation of the upper abdominal OAR, representing an advantage when compared to kV CBCTs (55). Favorable experiences regarding the visibility of metastases and primary liver cancer have been reported for both low and high field MR-linac hybrid devices (46, 49). Furthermore, the use of contrast agents or specific sequences enriches the standard positioning image and allows better visualization of the OAR. Liver specific contrast agents such as gadoxetic acid (*i.e.* Gd-EOB-DTPA or Gd-BOPTA) are eliminated through the biliary tract and lead to a bright appearance of the liver, therefore improving the contrast between healthy and tumorous liver tissue and offering a better visualization and characterization of the lesions in late hepato-specific phase (56). Such agents have also been used in the context of clinical online MRgRT; however, caution is warranted with the repeated application of contrast agents within a short time frame, and safety data are still scarce about possible toxicity. When clinically indicated, MR compatible fiducials may also be implanted as reference markers: platinum ones have the most favorable technical and logistic profile (57). Imaging and sequence comparison studies between diagnostic and hybrid MRI are still lacking, and the need to rely on standard diagnostic imaging, especially for target volume segmentation support, is currently still strongly suggested for MRgRT applications.

Primary Liver Cancers

HCC nodules show great variability in imaging characteristics and radiological aspects due to the varying content of substances. Their semeiotics in T1WI and T2WI is generally not constant, and the acquisition of dynamic contrast is a key factor for diagnosis and tumor characterization, especially to detect vascular invasion (58).

HCC usually shows early arterial phase enhancement and rapid washout in the portal venous (PVP) or delayed phases (DP), while it is generally hypointense in the hepatobiliary phase (HBP) (59). The use of T2WI and DWI may be useful to make differential diagnosis between uncommon hyperintense HCC presentations or focal nodular hyperplasia or other benign conditions. The semeiotics of HCC nodules in standard 0.35 T TRUFI imaging is mixed with prevalence of hyper-isointense aspect. **Figure 1** shows HCC lesions on hybrid MRgRT images for both high and low tesla units.

The radiological aspect of cholangiocarcinoma on MR imaging depends on the anatomical site and on its growth characteristics and may be successfully described using complex magnetic resonance studies including cholangiopancreatography, conventional T1WI, T2WI, DWI, and Dynamic Contrast Enhanced (DCE) sequences. Peripheral mass-forming intrahepatic presentations generally appear isointense or moderately hypointense in T1WI and hyperintense in T2WI, with restricted diffusion in DWI. Contrast enhancement is characteristically late and centripetal and may facilitate the differential diagnosis from other masses (*i.e.* HCC and metastases). Periductal infiltrating lesions are visible on T2WI showing hyperintense dilatation of the upstream ducts, while extrahepatic ductal forms generally

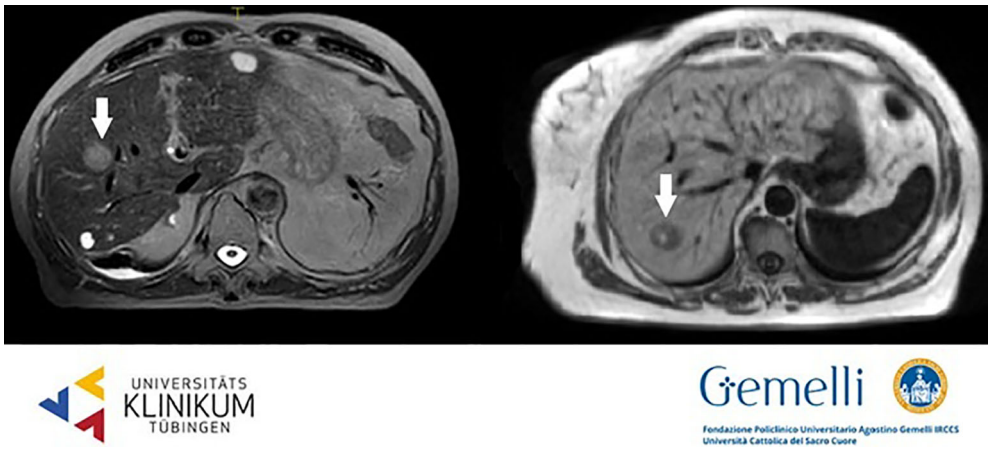

FIGURE 1 | HCC nodules on T2 weighted 1.5 T hybrid imaging (left) and on T1 weighted 0.35 T hybrid imaging (right).

appear as masses to be differentiated from pancreatic head adenocarcinomas (60). Cholangiocarcinomas are generally hypointense in TRUFI on 0.35 T hybrid units.

Secondary Lesions

Liver metastases are generally hypointense in the HBP, appearing as areas of loss of signal with respect to the enhanced normal liver parenchyma, due to cellular substitution (61). The radiological semiotics of secondary hepatic lesions may suggest the originating disease, thanks to specific image characteristics. Adenocarcinomas metastases appear hypointense in T1WI, slightly hyperintense in T2WI, with restricted diffusion and low apparent diffusion coefficient (ADC) values. The use of contrast agents generally discloses a hypovascularized central core accompanied by a hypervascularized external rim (62, 63). Pronounced hypervascularization in dynamic phases is characteristic also of neuroendocrine tumors (NETs); melanoma, thyroid, and renal cancer more often show a hypervascularized aspect (64–66). On the other hand, colorectal, lung, and breast cancer secondarisms generally appear hypointense compared to the enhancing normal liver parenchyma in PVP. Secondary liver lesions generally appear as hypo-isointense nodules in standard 0.35 T TRUFI positioning image (see **Figure 2**) (63).

Table 2 summarizes the sequences of more common clinical use for liver target volumes identification.

MRI BASED RT VOLUME SEGMENTATION

The standardized and accurate definition of target volumes and OAR has become an even more crucial factor in the MRgRT workflow. For instance a relevant organ at risk delineated erroneously too large might prevent sufficient target volume coverage in the daily adaptive workflow and, *vice versa*, severe toxicity may result if OARs are not delineated at their full extent.

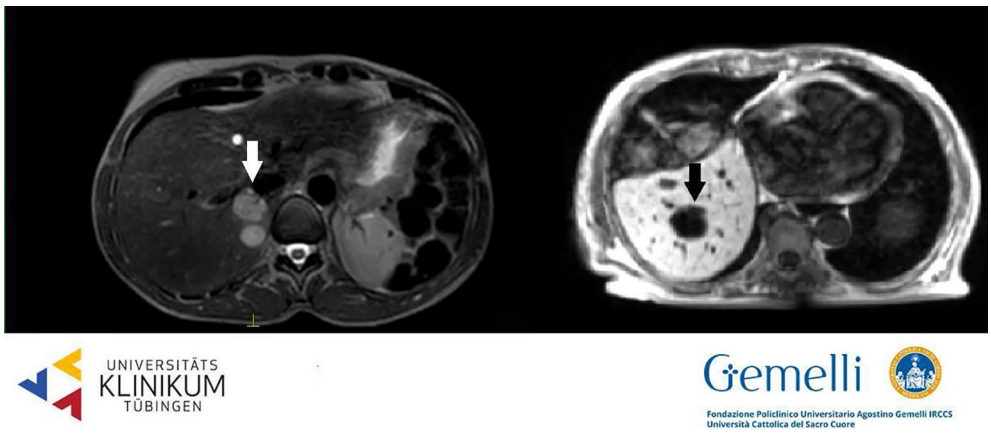

FIGURE 2 | Liver secondary lesions on T2 weighted 1.5 T hybrid imaging (left, hyperintense, from breast cancer) and on T1 weighted 0.35 T hybrid imaging (right, hypointense, from gastric cancer).

TABLE 2 | Liver lesions in the different MR sequences in current MRgRT clinical use.

Lesion	T1WI (non-CE)	T2WI	TRUFI (0.35 T)
Hepatocarcinoma	Hypointense	Iso-hyperintense	Iso-hyperintense
Cholangiocarcinoma	Hypointense	Iso-hyperintense	Iso-hypointense
Metastases	Hypointense	Hyperintense	Hypointense

CE, contrast enhanced.

For this reason, a panel of radiation oncologists and radiologists with experience in the field of online MR guided radiotherapy of the liver has recently published an atlas for OAR contouring in the upper abdomen (55). Dicom datasets with recommended delineations of upper abdominal OAR structures can be found at www.econtour.org. More specifically, when contouring the liver on MRI it is recommended to exclude the inferior vena cava and include the caudate lobe in order to achieve an appropriate quantification of functional liver tissue. Both structures are challenging to identify on non-contrast enhanced computed tomography simulation scans but can well be visualized on both T1WI and T2WI. Another structure that is sometimes poorly visible on CT scans is the common bile duct. *Post hoc* studies of hepatobiliary toxicities, such as biliary structures or elevated liver function tests after SBRT for centrally located tumors, suggest a dose effect for these toxicities (67). The common bile duct can be clearly seen on T2WI in most cases or on the HBP after the application of liver specific contrast agents. The delineation of this structure might help to prevent these toxicities by considering them during plan adaption and to further improve our knowledge about the dose–volume relationship in this anatomical site (68). Stomach, duodenum, and small bowel loops are the most critical OAR when high doses of radiotherapy are applied in the upper abdomen. In most instances a T2 weighted scan is the optimal sequence for their delineation; however due to motion artifacts caused by peristalsis there is still a need for optimized sequences in adaptive MR-linac workflows and OAR margin definition indications. The administration of a glass of water shortly before the treatment fraction may help in visualizing the stomach and the duodenum (that will appear hyperintense in TRUFI and T2 images), while the use of antiperistaltic agents (*e.g.* butylscopolamine) may reduce the motion related artefacts allowing a more efficient and reliable segmentation process.

MOTION MANAGEMENT FOR LIVER MRgRT

SBRT is characterized by the attempt to minimize PTV and to provide a rapid dose fall off towards the surrounding healthy tissues. Especially in liver SBRT, the main challenges are the proximity of the tumor to many vulnerable OARs such as the healthy liver, duodenum, stomach, bowel, kidneys, or spinal cord and the mobility of both the tumor and the surrounding OARs triggered by breathing-related motion or by changes in the filling status, anatomical arrangement or deformation of gastrointestinal organs (69). Organ motion in the abdominal region is greater than in other sites, with movements in the cranio-caudal direction of up to 4 cm, which is two to three times larger than the movements in the anterio-posterior or lateral directions (69, 70). This is often compensated by an increase in the irradiated internal target volume (ITV concept) (71), which on the other hand can be accompanied by the trade-offs of losing the potential gain of modern radiation techniques in sparing OARs. In liver radiotherapy, the post-interventional liver function can be predictive for patient survival (72). Therefore, adherence to radiation tolerance of normal liver tissue and keeping the associated risk of RILD to a minimum are of utmost importance.

Available motion management strategies to compensate for intrafractional breathing-related organ motion in conventional image-guided liver SBRT can be categorized into: 1) non-gated techniques (with or without mechanical abdominal compression) using the adoption of the ITV or mid-position concept; 2) respiratory-gated techniques, including use of a breath-hold 'immobilization' approach; or 3) real-time tumor tracking (73, 74). Due to the relatively poor soft tissue contrast in conventional SBRT using CBCT, frequently the tumor cannot be directly visualized, and implantation of fiducial markers next to the tumor or other surrogates is needed to facilitate image-guidance (75, 76).

In this setting, the application of MRgRT marks the beginning of a new era, as multiple features of this new technology may improve the application of liver SBRT and enable dose escalation strategies, and reduced doses to adjacent normal tissues. Besides the advantages of online treatment plan adaption strategies, which will be highlighted in the next section, the technology enables a direct visualization of the target—even during treatment delivery (4, 77). With currently available MR-linac systems, continuous real-time 2D-cine-MRI is used to assess tumor motion (2, 78). In future, also three-dimensional (3D) MR scans at an adequate resolution and frame rate to monitor fast motion might be available and further improve the applicability of MR guidance for intrafractional motion monitoring (*i.e.* 4D or respiratory correlated MR) (73). To date, the Viewray system also allows automated gating by using repeated fast planar cine-MRI in a sagittal plane with four to eight frames per second (2). This eliminates the need for invasive implantation of fiducial markers as well as the application of ITV in order to account for intrafractional motion (50).

Early experiences show promising results (8, 11, 46). Rosenberg et al. (11) report on a multi-institutional experience of MR-guided SBRT using a 0.35 T MR-linac system. Respiratory-gated SBRT was performed by using a voluntary breath-hold procedure without any external respiratory motion management system. Simulation with real-time sagittal TRUFI cine MRI sequences was used to evaluate tumor motion and to find a reproducible and tolerable breath-hold level. The breath-hold technique requires that the patient inhales to a specified threshold and successively holds the breath at a specific level of inspiration during delivery of every radiation beam. This enables minimization of tumor movement and allows for a reduction of the irradiated liver volume. While the breath-hold technique is

usually performed in deep inspiration for thoracic tumors, a shallow breath-hold or expiration breath-hold seems also feasible to mitigate target movement for upper abdominal tumors, like liver tumors. In this setting, the breath-hold technique has proven to be a safe and effective way to reduce tumor motion, resulting in an average intrafractional movement of <1 mm in all directions and an average cranio-caudal interfractional reproducibility of <4 mm (79, 80). Some authors reported on the implementation of an additional visual feedback for the breath-hold procedure using in-room screens or projectors (81, 82). This allows patients to see their live cine MR images including projections of target and gating boundary and, thus actively control their breathing.

During RT delivery, the 0.3 T MR-linac system can automatically gate the beam by using real-time anatomy structure tracking (83). For this purpose, a target structure is defined in the sagittal view of the volumetric MRI, and a surrounding gating boundary contour is created by adding an appropriate tracking margin. Usually, the gating boundary is equal to or less than the PTV margin. The tracking algorithm deforms the anatomical contour on every subsequent live cine MRI frame and compares it to the static boundary contour. If the anatomy of interest moves outside the boundary, the beam is stopped until the tracked anatomy returns into the boundary. The percentage of the target that may be outside the boundary before beam is shut-off can individually be adjusted. The vendor-defined specification for the gating latency of the 0.3 T MR-linac system is <500 ms (2).

The target structure used for tracking is usually the liver tumor itself. Nevertheless, some liver tumors are often poorly visualized, even in MR imaging. Therefore, the application of hepatocyte-specific contrast agents, such as gadoxetate disodium, is reported to significantly improve visualization of liver lesions during simulation and real-time MR-guided SBRT (84). If visualization is still not optimal, tracking can also be performed on surrogate structures, such as the portal vein, liver contour, or other anatomical structures (11). The Unity system is likely to have this capability soon, but at present can only gate the beam manually.

Taken together, MRgRT using a respiratory-gated SBRT with a breath-hold technique enables a completely non-invasive approach to treat liver lesions while reducing the irradiated volume of the uninvolved healthy liver tissue. Furthermore, the ability of MR-linac systems to provide direct visualization of the patient anatomy throughout the treatment fraction can also reduce interfractional and intrafractional uncertainties in target localization and allow dose escalation strategies (85).

ADAPTIVE APPROACHES FOR LIVER MRgRT

Adaptive radiotherapy (ART) emerged in the radiation therapy lexicon over 20 years ago, initially signifying a means to control daily set-up error using megavoltage portal imaging (86). However, the term now broadly signifies the process by which the delivered dose is monitored and modified during the course of treatment to ensure clinical acceptability and maximize clinical outcomes. Online ART specifically refers to the daily modification of the radiation treatment plan in response to observed changes in daily tumor and/or OARs anatomy, while the patient remains on the treatment table. This may adjust for tumor response (87) or inter-fraction tumor/OAR motion (51) and has the intent of maximizing the therapeutic index.

Online ART thus depends on high quality on-board imaging that is sufficient to visualize and delineate the target and/or OARs for daily plan re-optimization. Logically then, the clinical implementation of integrated MRgRT and MRI-guided online ART (MRgART) in 2014 (87) has led to the rapid expansion in use of online ART, including for liver tumors. MR-guided online adaptive radiotherapy can have several advantages over conventionally planned radiotherapy. The most established of these include target dose escalation, OAR dose reduction, and plan adjustment based on target response to treatment. Online adaptation through MRgART can allow target dose escalation and OAR dose reduction due to improved management of unpredictable inter-fraction motion. For patients with tumors near dynamic OARs, inter-fraction changes historically lead to uncertainty in the daily tumor/OAR geometric relationship. These uncertainties limit dose in order to maintain safety. In the upper abdomen, stomach filling, duodenal distension and motion, and small and large bowel motion may all lead to large changes in the proximity of liver targets to OARs (88). Online adaptation allows for daily plan adjustment in response to these changes to spare OAR dose while enabling confident delivery of ablative tumor dosing.

MRgART also enables plan changes to account for more predictable changes, such as tumor response over the course of therapy, or patient factors like weight loss or gain. However, it should be noted that given the additional time, personnel, and resources required to adapt a treatment plan at up to each fraction (89, 90), the tendency over the past six years of use has been implementation of MRgART mainly for SBRT or similarly hypo-fractionated courses, rather than for adaption for predictable changes occurring over a longer fractionation (91, 92). Thus, inter-fraction changes like day-to-day OAR motion are the more common driver of online adaptation in the current era, and most current data and experience with upper abdominal and liver MRgART is in this setting. As technology improves and time of delivery of MRgART shortens, use of MRgART may be more common in conventional fractionation schemas.

Given these specific advantages as well as the resources required for MRgART, patient selection is an important aspect of MRgART. With regard to the advantage of accounting for changing tumor/OAR geometry, tumors within 2 cm of the viscous gastrointestinal tract (*i.e.* peripheral liver tumors) are more likely to require plan adaptation than tumors surrounded by normal liver parenchyma (51, 52). This is due to the rapid dose fall-off with SBRT planning, wherein inter-fraction OAR motion has to occur within the higher dose gradients in order to

meaningfully affect potential OAR dose. This may be particularly important in patients with liver metastases, where dose escalation has been linked with improved local control (93). While HCC may be successfully treated at somewhat lower SBRT doses, nearer to point dose tolerances of the stomach and bowel (94), large changes in stomach and OAR filling can be observed that exceed reasonable planning OAR volume (PRV) construction for avoidance (88). Therefore, peripheral HCCs may benefit from online adaptation to maintain adequate tumor dose while minimizing risk to OARs.

Other primary liver cancers, like cholangiocarcinomas, may also benefit from daily plan adaptation in order to mitigate potential OAR injury. This adaptation, which may in turn allow for safe tumor dose escalation, has been correlated with improved overall survival in cholangiocarcinoma patients (95). This style of dose escalation requires less intentional, conservative underdosing of the tumor rind adjacent to OARs and could be performed instead of the conventionally fractionated, multiple dose level, PRV approach that many centers use to attempt tumor dose escalation while protecting OARs. Similarly, in hilar cholangiocarcinomas, MRgART has been shown to minimize dose to the stomach and duodenum that can otherwise occur from daily changes in stomach and duodenal distension and positioning (52). This may allow further dose escalation in this challenging location, which may improve local control, a key element of either definitive or bridge-to-transplant therapy in these patients. Higher dose delivery may be feasible here, as the common bile duct (CBD) is often permanently stented in these patients, which may mitigate long term biliary stenosis (96), or can alternatively be in the setting of daily monitoring of dose to uninvolved duct, as the CBD is well-visualized on both 1.5 and 0.35 T on-board images (55).

MRgART also requires new considerations in workflow, which can be separated into: 1. Simulation, 2. On-table pre-treatment, and 3. Beam-on time-frames. At the time of this writing, there are two commercial integrated MRgRT platforms capable of online ART: the Elekta Unity 1.5 T device and the ViewRay MRIdian 0.35 T system. For simulation, computed tomography imaging is typically still obtained for density information for initial and subsequent adaptive plans. Patients can then be additionally imaged on the treatment MR-linac, which is helpful to learn how well target and OAR anatomy will be visualized ahead of the on-the-fly portion of adaptive re-planning. Standard immobilization can be used (as long as devices are MRI compatible), which can also help to minimize the need to online adapt simply to adjust for gross positional changes. Reproducibility of imaging coil positioning should also be considered, with options like building the coils into immobilization devices or custom table-overlays used variably between institutions.

In contrast to CBCT based IGRT, patients typically do not require fiducials, as the tumor is well-visualized on the available sequences of both devices. Intravenous contrast hepatobiliary contrast agents can be used for simulation and have also been shown to be safe for daily use in the setting of SBRT fractionation in patients with adequate renal function (84). Acquisition of simulation images both with and without contrast can help identify the cases in which it will be necessary for daily online ART fractions and, conversely, spare its daily use in those cases where it is less impactful.

The two commercial platforms share a similarly structured, on-table adaptive workflow, with minor differences (97). Of note, the 1.5 T system has two "adaptive" workflows, an "adapt to shape" workflow, which is akin to the definition of online adaptation used in this writing and used on the 0.35 T system, and an "adapt to position" workflow. The "adapt to position" workflow is essentially an isocenter shift (*via* a shift in MLCs) to overcome the inability to shift the patient couch on the 1.5 T system and is not the focus here.

On each platform, the on-table component of MRgART fractions is initiated by acquisition of the daily, online volumetric MRI. Typically, this sequence will match the sequence used at simulation to minimize impact of imaging differences on perceived changes in anatomy-of-the-day. Next, the pre-treatment planning image is rigidly registered to the image of the day, generally to the centroid of the gross liver tumor volume, or to adjacent surrogate structures if the tumor is difficult to visualize (vascular structures, liver edge, *etc*). On the 1.5 T system, this is achieved through export to a separate treatment planning system (TPS Monaco) (98). On the 0.35 T system, this is on the dedicated/integrated online MRIdian TPS (1).

Next, on both platforms, the original contours are automatically propagated to the daily image using rigid (preferred for targets, when possible) and/or deformable registration. Physicians and therapists then edit the contours as needed to match the daily anatomy. To save time in contouring, contour adjustments for SBRT plans may focus on anatomy within a 2–3cm ring around the PTV, which captures the high dose fall-off region of interest for OAR sparing and has been shown to be sufficient for robust and fast plan re-optimization (48). Electron density is updated, either through contour-based bulk density override (0.35 T system) or application of the average electron density for each structure as identified from the simulation image (1.5 T system). The plan is then reoptimized, typically through an adjustment of beam weighting, segments, and fluence or mix thereof, with maintenance of the original beam angles. In both planning systems, this process is rapid within the order of seconds to several minutes (51, 98).

Online, pre-treatment quality assurance is then performed (99), and the original plan is compared to the online adaptive plan, with selection of the superior plan for delivery. It is key to note that formal dosimetric (*e.g.* dose metric or DVH) comparison should be used for the selection of the superior plan, as visual assessment of the plan alone, for the need for daily adaptation has been shown to be inadequate for identifying fractions benefitting from plan change (100). The beam-on component of ART on both MRgART systems utilizes real-time cine MRI monitoring and beam-gating. On the 0.35 T system, cine MR imaging is at a rate of eight frames per second and beam-gating is automatic, through a deformable

registration-based tracking algorithm (83). On the 1.5 T system, beam-gating is presently manual but still based on real time MRI target (or adjacent surrogate) monitoring (101). On both systems, breath-hold delivery may improve efficiency of treatment, and combinations of patient visual feedback and/or audio respiratory coaching have been utilized successfully. Specifics of motion management choices are discussed in more depth in the *Motion Management* section.

DISCUSSION

In the future, MRgART is likely to increase in both complexity and indication.

MR-only planning has been achieved in some settings (102) and may find ready application in liver patients in the setting of MRgRT. Future considerations also include personalized adaptation or dose prescribing based on MRI-specific imaging indications of tumor response, such as changes in diffusion restriction (103) or MRI tumor volumes during the course of treatment (104). However, standardization of imaging and methods for signal detection, as well as application to patient care, is needed for mainstream use (105). Ongoing and additional prospective clinical trial efforts are needed to establish the clinical benefit of MRgART in liver patients.

A future MRI-only liver SBRT workflow has advantages over the aforementioned CT–MR hybrid workflow, with the potential to improve overall efficiency. It requires replacement of planning CT with synthetic CT generated from the planning MRI (*i.e.* electron density mapping) through voxel-based methods, atlas based methods, or hybrid approach (106). This MRI-only workflow will reduce CT scanning to enable reduction of radiation dose and imaging costs with more efficient use of resources, and more importantly, avoid geometric uncertainties of MRI–CT co-registration through direct delineation of the target and OARs on MRI with improved geometric treatment accuracy (107). Inter- and intra-fractional treatment adaptation with fast auto-contouring algorithms, automated treatment planning, and automatic reconstruction of the delivered dose of the day cumulative dose delivered would facilitate and improve the accuracy of SBRT for liver cancer patients (108).

Several studies have demonstrated that higher doses of RT were correlated with improvement of tumor control and overall survival for many unresectable liver tumors (*i.e.* liver CRC metastases and hepatobiliary tumors) (40, 93, 95, 109). However the ability to deliver high-dose of RT to liver tumors adjacent to nearby luminal gastrointestinal organs and the requirement to spare sufficient un-involved liver to maintain synthetic liver function necessitate accurate liver cancer target delineation, precise RT planning, and real-time treatment adaptation to improve sustained local control while reducing the risk of toxicity. These challenges can be mitigated in part by MRI-based RT planning and delivery, when personalized dose escalation to liver tumors could be based on cumulative delivered doses to limiting OAR, rather than limiting the RT dose based on a single pre-treatment image.

MRgRT provides an elegant platform to investigate early biomarkers for tumor control and late toxicity, through repeated MR functional imaging obtained throughout a course of radiation therapy. DWI MRI is based upon differences in mobility of water protons in tissues and is useful for detection and characterization of focal liver lesion and assessment of tumor response to treatment. Advanced diffusion methods such as intravoxel incoherent motion (IVIM) may have potential for detection, staging, and evaluation of the progression of liver fibrosis and for liver lesion characterization (110). DWI has been studied as a potential imaging biomarker early during SBRT associated with long term local control. It has also been investigated as a biomarker for radiation related liver injury (103). Previous work has shown heterogeneous cell populations within individual tumors, and repeat DCE MRI scans throughout treatment were able to predict the change in hypoxia in preclinical model (111) Employing pre- and intra-treatment functional imaging provides an opportunity for further personalized treatment with optimization of SBRT dose on a daily basis to accommodate temporal heterogeneities in tumor, where SBRT dose escalation could target areas of highest biological resistance, while areas of good response undergo dose de-escalation, opening avenues for dose adaptation with improved therapeutic ratio.

Radiomics aims to utilize computational pipelines to extract the most informative features from radiological images routinely acquired in clinical settings. Recent computational advances have allowed deep neural networks (DNNs) to learn unique features with unprecedented performance for image classification (112), eliminating the need for hand-engineered features required for "conventional" radiomics analyses. The application of deep learning in the medical imaging field is in its infancy (112), with only a few studies that have applied DNN radiomics pipelines to predict patients' clinical outcomes (113–119). The plethora of MR images generated through an MRgRT radiotherapy system would create very large datasets capable of similar, if not improved, utility given the more visualization provided by MRI. The use of MRI-derived data combined with correlative biologic factors (*e.g.* genomics, metabolomics) and tumor microenvironment information will provide more understanding of tumor biology, implicating heterogeneous tumor subpopulations and their surrounding microenvironment as key factors in clinical outcomes and allow for a substantial degree of treatment personalization.

AUTHOR CONTRIBUTIONS

Conceptualization: LB and LD. Writing original draft preparation: LB, SC, CG, LH, AH, and AR. Writing—review and editing: LB, SC, CG, LH, AH, and AR. Supervision: LD. All authors contributed to the article and approved the submitted version.

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Adaptive Magnetic Resonance-Guided Stereotactic Body Radiotherapy: The Next Step in the Treatment of Renal Cell Carcinoma

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Adaptive MR-guided radiotherapy (MRgRT) is a new treatment paradigm and its role as a non-invasive treatment option for renal cell carcinoma is evolving. The early clinical experience to date shows that real-time plan adaptation based on the daily MRI anatomy can lead to improved target coverage and normal tissue sparing. Continued technological innovations will further mitigate the challenges of organ motion and enable more advanced treatment adaptation, and potentially lead to enhanced oncologic outcomes and preservation of renal function. Future applications look promising to make a positive clinical impact and further the personalization of radiotherapy in the management of renal cell carcinoma.

Keywords: MR-guided radiotherapy, renal cell carcinoma, stereotactic body radiotherapy, MR-linac, image-guided radiotherapy

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INTRODUCTION

Renal cell carcinoma (RCC) is the seventh most common malignancy in the world, where an estimated 400 000 people are diagnosed per year (1). North America has the highest worldwide incidence (age-standardized rate [ASR]: 12 per 100 000) followed by Western Europe (ASR: 9.8) and Australia/New Zealand (ASR: 9.2) (1). The rise in incidence of RCC since the 1980's has been estimated at approximately 0.5-1% per year, partly attributable to both the increased utilization of cross-sectional imaging leading to incidental findings of small renal masses, and a parallel increase in obesity in Western societies (2, 3). There has also been an increase in the median age of diagnosis (age 65), with the largest increase in patients 70 years or older (4).

Surgical resection remains the gold standard of care in patients with localized RCC. Oftentimes surgery is not possible in an elderly population with other competing medical comorbidities, such as chronic kidney disease (CKD), and carries significant risks of morbidity and/or mortality (5). As a result, options such as active surveillance (AS), or thermal ablation including radiofrequency ablation (RFA) and cryotherapy are considered viable strategies, as demonstrated by their inclusion within the American and European Urological Association guidelines (6, 7). However, tumor size,

location and proximity to the renal hilum/vasculature may limit surgical options and percutaneous ablative techniques that require anesthesia. Stereotactic body radiotherapy (SBRT) has emerged as a potential non-invasive option for inoperable patients. A pooled analysis from the International Radiosurgery Oncology Consortium for Kidney (IROCK) has demonstrated SBRT, on conventional conebeam CT (CBCT) linacs or robotic radiosurgery platforms, to be effective in terms of local control (98%), cancer-specific (92%), and progression-free survival (65%) at four years (8). Reported late toxicity (grade ≥3 less than 2%) is minimal, and the impact on renal function (average decrease of 5.5 mL per minute) is comparable to other nonsurgical strategies (9, 10). SBRT has been demonstrated to be effective regardless of tumor size (a limitation of thermal ablative techniques) (11), in patients with solitary kidneys (a limitation for CN or PN) (12), and is well tolerated in an older, medically frail population (13). Prospective trials of RCC SBRT including FASTTRACK II from the Trans-Tasman Radiation Oncology Group (TROG) and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) (NCT02613819) and RADSTER from Canada (NCT03811665) are ongoing or have completed patient recruitment with results forthcoming in the next few years.

A closer look at the existing pooled analyses suggests there may be further gains to be made. Limitations of these analyses include the absence of pre- and post-treatment comorbidity assessment, retrospective data collection with possible under-reporting of toxicity, and short follow-up. Single fraction SBRT was associated with better progression-free and cancer-specific survival and distant control compared to multi-fraction SBRT, however, patients experienced more nausea. Patients who received a single fraction had better baseline renal function, but demonstrated a trend toward a greater decline compared to patients receiving multiple fractions (8). A further analysis of patients treated with large tumors (>4cm) showed a mean decline in renal function of -7.9 mL per minute; of which a significant proportion of patients had pre-existing stage 3 CKD (11). Could MRgRT permit more utilization of single fraction SBRT (for large tumors in particular) with the potential of further improving oncologic outcomes beyond local control and minimizing the impact on renal function in medically comorbid and inoperable patients?

TECHNICAL CHALLENGES OF IRRADIATING RCC

RCC is traditionally perceived to be radioresistant to conventionally fractionated radiation; however, studies using hypofractionated doses of radiotherapy (RT) demonstrated exponential cell kill (14, 15). Historically large margins were used to ensure that the tumor was irradiated, thus limiting the escalation of dose that could achieve tumor control. This is in part due to large and complex kidney motion (16–19), and highly radiosensitive tissues that surround the kidney and tumor itself, such as the small and large bowel, duodenum and the renal parenchyma. With advances in pretreatment imaging, treatment planning, and implementation of image-guided radiotherapy (IGRT), SBRT was introduced and allowed for delivery of high doses to the tumor. On conventional CBCT-linacs, the internal target volume (ITV) is typically estimated from 4D computed tomography (4DCT) and is the most common passive motion management technique. It represents the treatment volume delineated on all phases of the 4DCT, and is incorporated within the planning target volume (PTV). ITV is based on the assumption that tumor motion estimated during pre-treatment 4DCT acquisition is representative of the motion throughout RT treatment. However, this approach is limited by the inherent low soft-tissue contrast of 4DCT (which may lead to visualization and delineation errors of renal tumors) and on-board CBCT [potentially underestimating intrafraction motion due to respiratory variations (20) and drift (21)], which impacts the reliability of IGRT. As such, larger PTV margins, implanted fiducial markers, or rigid/deformable image registration with multiphasic CT/MRI are options to decrease these uncertainties. Cusumano et al. (22, 23) analyzed the respiratory-induced motion of thoracic and abdominal lesions based on 2D cine-MR (4 images/second) acquired with a 0.35T MR-linac (Viewray, Oakwood Village, OH). In a subset of four kidney patients, the range of 4D-CT motion was 2-9mm craniocaudal (CC) and 1-5mm anteroposterior (AP); the range of MR simulation motion was 5-10mm (CC) and 2-3mm (AP); and 4-9mm (CC) and 2-3mm (AP) during treatment delivery. The data suggests that reliability of the ITV approach may be lower in the abdominal region due to limitations of low soft-tissue contrast and target delineation with 4DCT, and that additional margins of 3mm CC and 2mm AP are required to ensure that renal lesions remain within the ITV for greater than 95% of the time during treatment.

THE POTENTIAL OF ADAPTIVE MR-GUIDED RADIOTHERAPY FOR RCC

MR-guided radiotherapy (MRgRT) is a new treatment paradigm that provides high-definition soft-tissue contrast which permits direct visualization of tumors and adjacent radiosensitive organs-at-risk (OAR). MRgRT offers real-time, online monitoring of tumor motion through the different phases of the respiratory cycle and the opportunity for daily adaptation – optimization of tumor targeting and OAR sparing, and dose delivery based on the anatomy from the daily acquired MRI. This may potentially lead to PTV margin reduction and improving the therapeutic ratio. The advantages of online adaptive MRgRT and in which clinical case scenarios maximum benefit will be achieved is yet to be determined.

The MRIdian 0.35T Co-60 MR-linac (Viewray, Oakwood Village, OH) workflow entails patients undergoing both a high-resolution volumetric MR scan and a planning computed tomography (CT) scan with a breath-hold. The CT scan is used for dose calculation purposes and to verify tumor size and shape. The GTV and OARs are delineated on the planning MR image. A PTV is generated by adding a 3 to 5mm margin to the GTV. Daily MRIs are fused with the planning MRI for online

adaptation and reoptimization. The system utilizes cine imaging at 4 frames per second in a sagittal plane for real-time anatomic tracking, deformable registration and respiratory-gated, visual patient feedback beam control. The tracking algorithm deforms the anatomical contour on every cine frame and compares it to the gating boundary contour, typically the PTV. Radiation delivery is stopped if the target moves outside the gating boundary, and resumes when it returns to treatment portal (24–27). Early work with lung and abdominal tumors with this system demonstrates at least 95% geometric coverage of GTV (28), and plan adaptation to enhance OAR sparing or to increase PTV coverage on a fraction-by-fraction basis without an increase in acute toxicity (29).

Recently Timmeren et al. (30) retrospectively examined treatment plan quality during the online adaptive re-planning process with a 0.35T Co-60 MR-linac. The MR-guided online adapted plans (n=238) to various targets were compared to the reference plans. The re-optimized plans achieved comparable dosimetric quality to the reference treatment plans, and OAR doses were either comparable or decreased across various tumor sites. The average adaptation time was 24 ± 6 minutes.

Members of the Elekta MR-Linac consortium contribute to the Momentum study (NCT04075305) (31) which is a prospective registry to capture all patient-related data as well as technical data to facilitate the development and implementation of MRgRT. Some patient selection and workflow criteria have been outlined by Hall et al. (32) in their treatment of liver and pancreas cancers using the Unity 1.5T system (Elekta, Stockholm, Sweden). A patient may be a potential candidate for MR-Linac radiotherapy if their lesion is difficult or impossible to visualize on a non-contrast CT, the lesion is in close proximity (within 1 cm) of a radiosensitive normal structure, and the patient is amenable to clinical trial participation. The 1.5T MR-linac provides two workflow solutions, namely, the adapt-to-position (ATP) or adapt-to-shape (ATS) workflows as previously described (33). The ATP workflow is a dose re-calculation after an image fusion based on the daily MRI, but it does not involve re-contouring on the daily MRI. It is ideal for those scenarios where there is minimal inter-fractional variation, a low chance of size variations and a reasonable distance between a mobile OAR and the target. The ATS workflow involves re-contouring and re-optimization of a new treatment plan based on the daily MRI. The ATS workflow may be ideal in a scenario where inter-fractional variations could be significant, such as a rapidly changing tumor size or close proximity to air cavities or mobile gastrointestinal structures.

Hall et al. (32) recently reported on ten patients (13 targets) treated with MRgRT for primary and secondary tumors of the liver and pancreas with a 1.5T MR-linac. Patients underwent 4DCT and MRI simulation, and an ITV method for motion management was used based on the 4DCT image dataset. PTV margins ranged from 3 to 5 mm. Daily adaptation was accomplished with the acquisition of pretreatment 4D MRIs, where motion-averaged or mid-position images were reconstructed and used for plan optimization, with either an ATP or ATS approach. The decision to use ATS was based on tumor proximity (3-5mm) to a mobile OAR (luminal GI structure) with variable daily position, proximity to an air cavity, and variable tumor size and position. Real-time monitoring of the target during treatment was done with cine MRIs in three perpendicular planes through the centre of the PTV. The median treatment time for the ATS workflow was 64 minutes. Currently, only free-breathing methods of motion management (with or without abdominal compression) are clinically feasible on the 1.5T MR-linac, while gating solutions are in preparation.

It is a natural evolution to apply MRgRT for kidney tumors alongside other abdominal/pelvic targets that share the same adjacent radiosensitive OARs (duodenum, small bowel, large bowel). The high-definition soft-tissue contrast of MRgRT permits better visualization of kidney substructures — such as the renal hilum (vasculature and collecting system) and parenchyma — that are hard to differentiate with conventional cone beam CT-guided radiotherapy, which may lead to increased tissue sparing and preservation of renal function.

EARLY CLINICAL EXPERIENCE WITH MR-GUIDED RADIOTHERAPY FOR RCC

Rudra et al. (34) published the first case report of a RCC patient that was treated with a 0.35T Co-60 MR-linac utilizing an end-expiration gating technique to deliver a dose of 40 Gy in 5 fractions. The treatment target was the GTV surrounded by a 5 mm gating boundary. The larger gating boundary resulted in less beam-on interruption and shorter treatment times, at the expense of irradiating more normal tissue. Typical gating margins ranged from 3 to 5 mm. For treatment planning 4D CT and MRI data sets were fused for contouring and dose calculation. The patient had lung and brain metastases, declined cytoreductive nephrectomy and continuation of nivolumab, and was treated with SBRT for the purpose of cytoreduction. No acute or late toxicities were reported, and the tumor and renal function remained stable 6 months after SBRT.

Tetar et al. (35) are the first group to report the outcomes of 36 primary RCC patients treated to a dose of 40Gy in 5 fractions on a 0.35T Co-60 MR-linac. The mean age of the cohort was 78.1 years and tumor diameter was 5.6cm (T1a: 5 patients; T1b: 23 patients; T2a: 8 patients). With a median follow-up of 16.4 months, the 1-year local control was 95.2%, freedom from progression was 91% and overall survival was 91.2%. One patient experienced acute grade ≥2 nausea, and no other acute or late toxicities were reported. Baseline mean eGFR was 55.3 mL/min/1.73 m^2 (SD ±19.0), and the mean decline in eGFR post-MRgRT was 6.0 mL/min/1.73 m^2. While the follow-up interval is short, oncologic outcomes and preservation of renal function in this cohort of mainly large tumors are favorable and consistent with a recent analysis of RCC SBRT (8, 11).

Prior to the delivery of each treatment fraction patients completed a short breath-hold MR scan, rigid registration was performed on the GTV and the OAR contours were propagated to the daily MRI scan using deformable registration. Routine plan re-optimization was undertaken where the treating radiation oncologist adjusted the GTV and OAR contours within 2 cm of the PTV. A baseline IMRT plan was recalculated on the new

anatomy from the daily MRI (predicted plan), and then re-optimized using the target and OAR optimization objectives of the baseline plan (re-optimized plan). The priority of plan re-optimization was to minimize high dose to OARs, even at the expense of decreased PTV coverage. The re-optimized plan was used for treatment delivery. MRgRT was delivered with respiratory gating where the gated structure was either the kidney itself, or the primary tumor if visible. Gating was augmented by visual and/or auditory feedback where patients were able to visualize the gated structure and the gating boundary, generally corresponding to the PTV (3mm). Treatment times for these patients ranged from 30–45 minutes for real time contour propagation, plan re-optimization and treatment delivery. **Figure 1A** shows a predicted and re-optimized plan and DVH for one treatment fraction of a right-sided RCC that highlights the improvement in GTV coverage and sparing of the duodenum and large bowel with plan adaptation.

The University of Texas MD Anderson Cancer Center is building experience in the treatment of primary kidney tumors and metastatic lesions within the kidney parenchyma on a 1.5T MR-linac. In collaboration with the urology department, non-operable RCC patients are currently being enrolled into the MRI-MARK trial evaluating the feasibility and effectiveness of MRI-based SBRT at a dose of 42 Gy in 3 fractions to the gross tumor volume (NCT04580836). An ITV method for motion management is employed and daily adaptation is done with the acquisition of pretreatment free-breathing T2 MRIs, followed by an adapt-to-position (ATP) or adapt-to-shape (ATS) workflow. Monitoring is achieved using real-time cine MRI with 3 orthogonal planes through the PTV during beam-on. **Figure 1B** shows the dose distribution for a left mid-upper pole RCC, and a DVH demonstrating the ability to achieve equivalent target coverage and OAR sparing with a MR-linac and standard VMAT treatment plan. With ATS plan adaption, GTV and PTV coverage can be improved while maintaining OAR sparing.

FUTURE OPPORTUNITIES

Therapies maximizing nephron-sparing is a priority for RCC patients in whom the prevalence of CKD is high (36). More efficacious and safer SBRT can be achieved with dose escalation

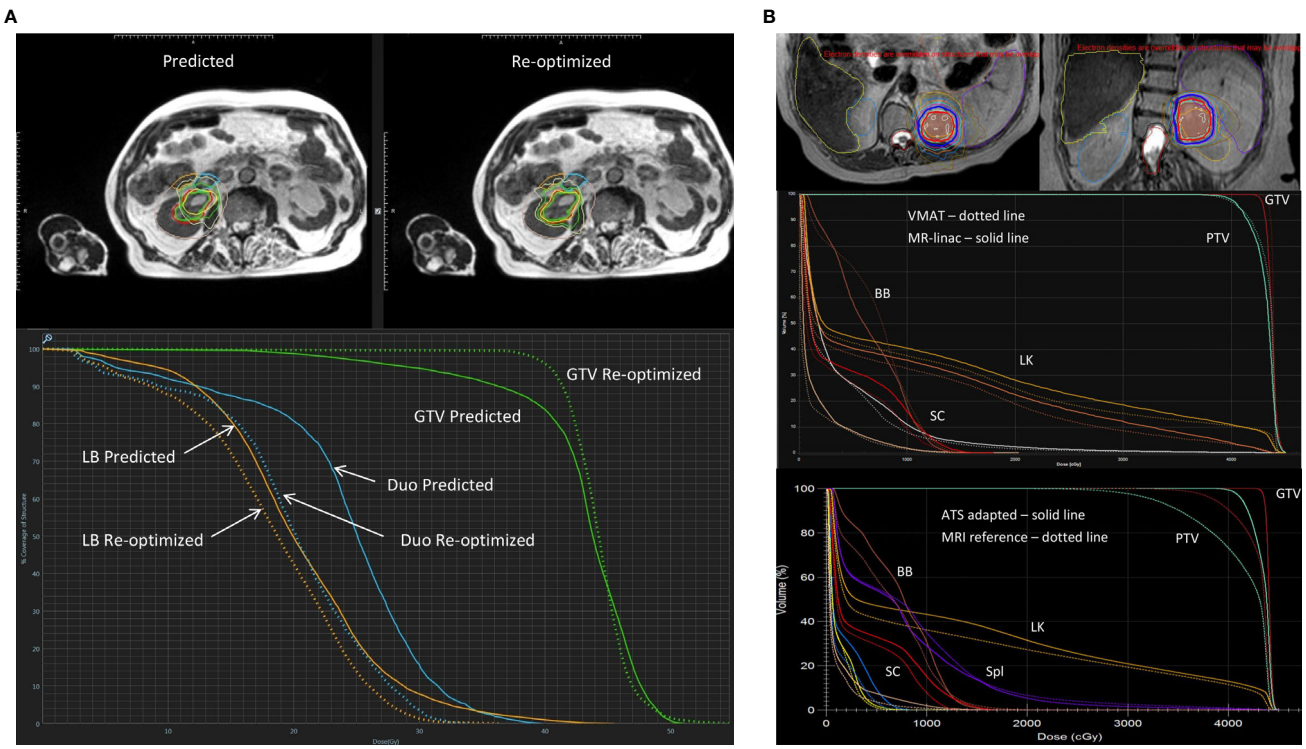

FIGURE 1 | Representative MRgRT treatment plans for RCC patients with **(A)** 40 Gy in 5 fractions on a 0.35T MR-linac (MRIdian, ViewRay, Oakwood Village, OH) and **(B)** 42 Gy in 3 fractions on a 1.5T MR-linac (Unity, Elekta, Stockholm, Sweden). **(A)** Top panel showing axial MRIs of a predicted and re-optimized plan of a right-sided RCC: GTV (green contour), duodenum (blue contour) and large bowel (orange contour); Bottom panel showing the corresponding DVH of the predicted (solid line) and re-optimized (dotted line) plans with improved GTV (green) coverage, and sparing of the duodenum (Duo - blue) and large bowel (LB - orange). *Reproduced with permission from AME Bruynzeel (Amersterdam UMC).* **(B)** Axial (left) and coronal (right) MRI treatment plan of a left-sided RCC showing ITV (brown color wash) and PTV (light green color wash) with isodose lines: 42Gy (red) and 36Gy (blue); Middle panel showing a DVH of VMAT (dotted line) and 1.5T MR-linac treatment plans (solid line); Bottom panel showing a DVH of an ATS adaptive (solid line) and reference plan (dotted line) with improved ITV (dark red) and PTV (light green) coverage, and equivalent sparing of the left kidney (LK – orange), spleen (Spl – purple), bowel bag (BB – brown) and spinal cord (SC - bright red). *Reproduced with permission from C Tang (MD Anderson Cancer Center)* (31).

and a reduction in margins, and requires MRgRT systems to advance with enhanced MRI sequences, intrafraction tracking and gating, and treatment adaptation. Developmental work in these areas is ongoing.

Al-Ward et al. (37) evaluated and quantified the potential radiobiological advantages of tumor tracking using the 1.5T MR-linac (Unity, Elekta, Stockholm, Sweden) for abdominal tumors (3 liver, 3 pancreas, 3 kidney). The investigators applied two planning methods, the conventional ITV method and a simulated tracking method (STT). The STT method was developed initially for lung tumor tracking in an MR-Linac and accounts for 8 phases of the breathing cycle, where more weight is applied to those phases where more time is spent. Similar methodology was then applied to the abdominal/pelvic targets. The average reduction in normal volume irradiated for kidney tumor patients due to tracking was 26.9%. The authors report that a normal tissue complication probability (NTCP) benefit due to tracking, was observed in 26% of the data. For all three disease sites, the maximum NTCP improvements were for the normal kidney, the bowels and the duodenum, with reductions in associated toxicities of 79% (radiation nephropathy) (38, 39), 69% (stricture/fistula) (38, 40) and 25% (ulceration) (38, 41), respectively. Even though this was a simulation study using a well-validated planning system, it indicates the potential benefits, in a best case scenario, that may be achieved in the reduction of side effects and/or an increase in tumor control probability if real-time tumor tracking is implemented (**Figure 2**).

Prins et al. (21) evaluated two motion management techniques, tumor trailing and respiratory tracking, in 15 RCC patients simulated for single-fraction, MRI-based SBRT within a 25-minute treatment time with free breathing. The largest respiratory tumor motion was observed along the CC direction with a median 95% maximum amplitude of approximately 12mm. Without mechanical immobilization, intrafraction drift accounted for 75% of the total intrafraction motion margin for online mid-position-based SBRT treatments. The described study, and a previous dose accumulation study highlight the importance of accounting for intrafraction motion and its impact on dose accumulation. These studies strengthen the case for online motion monitoring and real-time plan adaptation (21, 42). In a free-breathing treatment scenario the margin calculations show that a 6.1mm PTV margin would be required to account for the systematic and random errors of drift and respiratory motion, and could be reduced to 1.5mm with tumor trailing.

Further technical development will enable the opportunity to increase the utilization of single fraction SBRT for RCC (small and large) and enable future comparative studies to thermal ablative procedures. The next step in the evolution of MRgRT for RCC will be the ability to treat: multiple targets in the ipsilateral and/or contralateral kidney; oligometastatic (43) or oligoprogressive metastases{Palma, 2020 #677;Cheung, 2020 #687} (44) simultaneously; and large primary lesions in metastatic RCC (mRCC) that are not amenable for upfront cytoreductive nephrectomy (CN). With respect to the last scenario, results from the SURTIME (45) and CARMENA (46) trials, have led to a decrease in CN for International Metastatic RCC Database Consortium (IMDC) intermediate- and poor-risk patients. Based on the results of the Checkmate-214 trial (47), first-line treatment of mRCC is now combination immunotherapy with ipilimumab and nivolumab in intermediate/poor risk patients compared to sunitinib previously. "Cytoreductive' SBRT to the primary kidney lesion may be a novel treatment strategy to induce an enhanced and synergistic systemic anti-tumor immune response (an abscopal effect). This has been observed in patients with

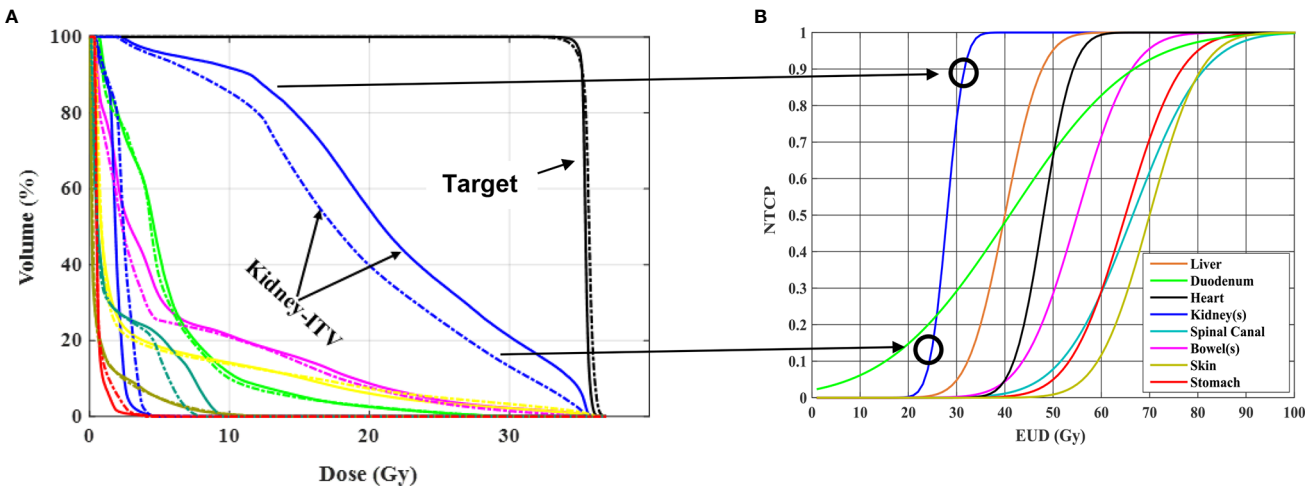

FIGURE 2 | Radiobiological impact of RCC motion tracking in **(A)** and patient treatment in **(B)** both utilizing a 1.5 T MR-linac Unity system (Elekta, Stockholm, Sweden). **(A)** *Adapted with permission from Al-Ward et al.* (37). On the left are shown DVHs resulting from two different treatment planning methodologies, one accounting for the ITV method of motion management (solid curve) and the other accounting for tumor tracking (dashed curve) for one of three kidney patients investigated. The sparing in irradiated normal kidney by using tracking results in a reduction in predicted normal tissue complication probability as shown on the right. Such reduction can be viewed as a way to reduce normal kidney toxicity or a way to maintain current toxicity but increase the dose delivered. This is simulated data representative of an ideal case scenario, indicating the potential benefits that could be achieved using an MR-guided motion tracking delivery strategy.

melanoma receiving anti–CTLA-4 therapy (48) as well as patients with RCC (49, 50). Putative mechanisms for this response include immune stimulation by novel neoantigens or pre-existing antigen-presenting cells, upregulation of calreticulin and $CD8^+$ proliferating T cells and other key immune-modulating cytokines (51, 52). The combination of nivolumab/ipilimumab along with cytoreductive SBRT to the primary lesion for mRCC is currently being evaluated in a randomized, phase II clinical trial (CYTOSHRINK NCT04090710) (53). MRgRT within this treatment paradigm may improve the therapeutic ratio by maximizing tumor coverage (generally large or unresectable lesions) while minimizing dose to OARs and the risk of combined radiation-immunotherapy treatment-related toxicities (for example, acute kidney injury and progression of CKD). Functional MRI for the diagnosis and prediction of treatment response for RCC are areas of ongoing investigation (54). Acquiring functional imaging studies on a 0.35T and 1.5T MR-linac during treatment is feasible (32, 55, 56). With consensus guidelines for image acquisition and quantification (57), MRgRT offers a unique opportunity to assess novel imaging biomarkers of response and toxicity in conjunction with serological correlates during SBRT alone or in combination with immunotherapy.

SUMMARY

The role of MRgRT in the treatment of RCC continues to evolve. MRgRT can potentially facilitate dose escalation and smaller treatment margins by overcoming the challenge of complex kidney motion, and reduce treatment-related toxicities by carefully evaluating and sparing critical OARs in real time. In the primary setting, this technology will help advance the use of SBRT for small and large renal tumors with potentially less renal toxicity, and improve the therapeutic ratio which will facilitate future comparative effectiveness studies versus other ablative modalities. In the metastatic setting, the benefits of MRgRT for oligometastatic or oligoprogressive tumors, and in combination with immunotherapy, may even be more pronounced where online tumor monitoring and daily adaptation to optimize dose delivery and OAR sparing may further mitigate toxicity. Such an approach would allow for potentially more effective combined modality therapy and brings us closer to realizing the promise of high-precision and personalized medicine in the field of radiation oncology.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical approval was not provided for this study on human participants because this perspective highlights previously published and ongoing studies that have received local ethics approval. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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REVIEW
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Magnetic Resonance Guided Radiation Therapy for Pancreatic Adenocarcinoma, Advantages, Challenges, Current Approaches, and Future Directions

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Introduction: Pancreatic adenocarcinoma (PAC) has some of the worst treatment outcomes for any solid tumor. PAC creates substantial difficulty for effective treatment with traditional RT delivery strategies primarily secondary to its location and limited visualization using CT. Several of these challenges are uniquely addressed with MR-guided RT. We sought to summarize and place into context the currently available literature on MR-guided RT specifically for PAC.

Methods: A literature search was conducted to identify manuscript publications since September 2014 that specifically used MR-guided RT for the treatment of PAC. Clinical outcomes of these series are summarized, discussed, and placed into the context of the existing pancreatic literature. Multiple international experts were involved to optimally contextualize these publications.

Results: Over 300 manuscripts were reviewed. A total of 6 clinical outcomes publications were identified that have treated patients with PAC using MR guidance. Successes, challenges, and future directions for this technology are evident in these publications. MR-guided RT holds theoretical promise for the treatment of patients with PAC. As with any new technology, immediate or dramatic clinical improvements associated with its use will take time and experience. There remain no prospective trials, currently publications are limited to small retrospective experiences. The current level of evidence for MR guidance

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in PAC is low and requires significant expansion. Future directions and ongoing studies that are currently open and accruing are identified and reviewed.

Conclusions: The potential promise of MR-guided RT for PAC is highlighted, the challenges associated with this novel therapeutic intervention are also reviewed. Outcomes are very early, and will require continued and long term follow up. MR-guided RT should not be viewed in the same fashion as a novel chemotherapeutic agent for which dosing, administration, and toxicity has been established in earlier phase studies. Instead, it should be viewed as a novel procedural intervention which must be robustly tested, refined and practiced before definitive conclusions on the potential benefits or detriments can be determined. The future of MR-guided RT for PAC is highly promising and the potential implications on PAC are substantial.

Keywords: MRI guidance, pancreatic image–guided RT, pancreatic cancer and radiation therapy, pancreatic cancer, MR-guided RT, MR-guided radiation therapy

INTRODUCTION

Pancreatic adenocarcinoma (PAC) has some of the worst treatment outcomes for any solid tumor (1). Median overall survival (OS) remains absolutely dismal for the vast majority of patients afflicted with PAC. It has risen to the fourth leading cause of cancer death in the United States (US), approaching colon and rectal cancer (1). In the next fifteen years, the projected impact of PAC is expected to increase, placing it as one of the top three causes of cancer death by 2030 (2). Radiation therapy (RT) remains controversial in PAC (3). On the one hand, RT is a highly compelling treatment strategy for PAC. Currently RT is successfully applied as a single modality, or in combination with systemic therapy, in curative treatment strategies in most adenocarcinomas and other tumors (4). On the other hand, RT in PAC is challenging due to the proximity of various radiosensitive normal structures like the duodenum, bowel and stomach. Deposition of curative RT doses while sparing the adjacent normal tissues is challenging with conventional RT techniques as the tumor and surrounding structures are highly mobile and difficult to see on CT based imaging. For a long time these limitations have hampered the use of curative RT doses on PAC causing somewhat modest treatment results when using RT in PAC. Recently MR-guided RT has emerged as a potential strategy to improve the therapeutic index of RT (5–8). For a variety of reasons, the MR-guided method seems optimally suited for the treatment of PAC. We sought to summarize and place into context the currently available literature on MR-guided RT for PAC. We highlight the potential promise, but also the challenges associated with this novel therapeutic intervention.

METHODS AND LITERATURE REVIEWED

A literature search was conducted using PubMed and Google Scholar to identify manuscript publications since September 2014 that specifically used MR-guided RT for the treatment of PAC. The goal of this search was to include manuscripts that describe the treatment of patients using FDA approved MR-guided RT technology. Search terms included: MR guided radiation and pancreatic cancer, MRI and RT and pancreatic cancer, image guided radiation therapy and pancreatic cancer, IGRT and pancreatic cancer. Over 300 search results were individually reviewed and multiple "similar article" links were subsequently referenced and also reviewed. Articles that merely incorporated MRI in the treatment planning process were excluded. Articles considered to be case reports (fewer than 3 patients) were excluded. Articles devoted purely to dosimetric feasibility were also excluded. Clinical outcomes of these series are summarized, discussed, and placed into context of existing pancreatic literature. Attention was given to dose constraints, which are summarized in **Table 1**.

DISCUSSION

MR-guided RT holds theoretical promise for the treatment of patients with PAC. As with any new technology, immediate or dramatic clinical improvements associated with its use will likely take time and experience. MR-guided RT should not be viewed in the same fashion as a novel chemotherapeutic agent for which dosing, administration, and toxicity has been established in earlier phase studies. Instead, it should be viewed as a novel procedural intervention which must be robustly tested, refined and practiced before definitive conclusions on the potential benefits or detriments can be determined (15).

Controversies in the Use of RT for PAC

There are several reasons for the seemingly intangible capacity of RT to present itself as a durable and consistently curative modality for PAC. First, and perhaps most relevant, is the high propensity for PAC to metastasize. When the majority of patients develop distant metastatic disease, the ability for a local modality, such as surgery or RT, to demonstrate meaningful improvements in OS, is difficult. Proof of the

TABLE 1 | Select clinical series to have applied MR guided radiation therapy to pancreatic cancer.

Author	N Panc CA	RT Dose/description	Bowel Constraints Applied	Conclusions/Toxicities Reported/Clinical Outcomes	Citation
Bohoudi et al. (9)	10	40 Gy in 5, max doses up to 50 Gy in 5, tumor + 5 mm margin	*Duodenum, Stomach, Small Bowel:* V33Gy < 1 cm^3 V25Gy < 20 cm^3	• Clinicians can review and adjust contours within 3 cm from the PTV, both feasible and safe • Faster treatment planning strategy is discussed	(9)
Henke et al. (10)	5/20	50 Gy in 5, goal of 95% coverage by 95% prescription dose, tumor + 5 mm margin	*Stomach Max:* V33 ≤ 0.5 cm^3 *Duodenum Max:* V35 ≤ 0.5 cm^3 *Small Bowel Max:* V30 ≤ 0.5 cm^3 *Large Bowel Max: V35* ≤ 0.5 cm^3	• SMART is clinically deliverable and safe • Very low rate of toxicity	(10)
Rudra et al. (11)	44	40-55 Gy in 25-28 fractions (n=13) 30-35 Gy in 5 fractions (n=6) 40-52 Gy in 5 fractions (n=16) 50-67.5 Gy in 10-15 fractions (n=9)	Range of institutional constraints included in supplement	• High dose (BED_{10} > 70) had improved 2 year overall survival, 49% versus 30%, p = 0.03 • Freedom from local failure was 77% in the high dose versus 57% in the standard dose • Grade 3 GI toxicity in 3/44 patients, all in standard dose	(11)
Chuong et al. (12)	35	35-50 Gy in 5 fractions, gross nodes also treated. 120%-130% dosimetric hot spots were included, provided OAR constraints met. 20 patients treated with ENI to celiac, SMA, and SMV to same dose as tumor	*Duodenum, Stomach, Small Bowel:* V35 Gy < 0.5 cm^3 V40 Gy < 0.03 cm^3 *Large Bowel:* V38 < 0.5 cm^3 V43 < 0.03 cm^3	• Median treatment time 83 min (56–108) • Five patients underwent surgery, 1 CR, 2 NCR • 1 year local control was 87.8% • Median time to local progression 7.4 months • 1 year DMFS was 63.1% • 1 year PFS/median PFS 52.4%/7.9 months • Median OS was 9.8 months (from completion of RT) • Acute grade 3 toxicity 2.9%, Late grade 3 toxicity 2.9%	(12)
Hall WA et al. (13)	3/10	Mostly recurrent PAC, previously treated with RT, patients were given 25-35 Gy in 5 fractions	*Stomach:* Max dose of 34 Gy to 0.03 cm^3 *Duodenum:* Max point dose of 34 Gy to 0.03 cm^3, 33 Gy < 1 cm^3, ideal-V20 < 20 cm^3, V26.5 < 5 cm^3 *Small Bowel:* Max point dose of 34 Gy to 0.03 cm^3, ideal-V20 < 20 cm^3, V26.5 < 5 cm^3 *Colon*: Max dose less than 34 Gy to 0.03 cm^3.	• Feasibility was demonstrated for this cohort using 1.5 Tesla MR Linac • Quantitative MRI can be acquired during treatment without longer table times • Longer term follow up needed for clinical outcomes such as late toxicity, OS, and local control	(13)
Hassanzadeh et al. (14)	44	50 Gy in 5 fractions, goal of 95% coverage by 95% prescription dose	*Esophagus, Duodenum, Small Bowel, Stomach Large Bowel*: V36<0.75 cm^3 for MR Linac 0.5 cm^3	• Late grade 3 GI toxicity was 4.6% • Median OS was 15.7 months • One year local control was 84.3%	(14)

PAC, pancreatic adenocarcinoma; n, number of pancreatic cases included; CR, complete response; NCR, near complete response; DMFS, distant metastases free survival; PFS, progression free survival; NR, not reported; SMA, superior mesenteric artery; SMV, superior mesenteric vein; OAR, organs at risk; GI, gastrointestinal.

benefit of RT could be accomplished, but it would require comparative trials of large numbers of patients who survive long enough to demonstrate the benefit of durable local control. Given that the majority of patients with PAC will die of distant metastatic disease progression such trials are difficult and have not been conducted. Regardless of how optimally local control is achieved, this will have been pursued in vain if a patient dies of distant metastatic disease. Despite this, distant metastatic disease is not realized in all patients with PAC, as one third of patients with PAC will die of predominately local disease progression (16). As systemic therapy has become more effective with both cytotoxic approaches and precision medicine strategies, this percentage will likely increase (17, 18). Maximizing local therapy will therefore become increasingly important for patients with PAC and will potentially lead to better OS in an era of more effective systemic therapies. Local

progression causes morbidity, which is difficult to treat. Effective local therapies can reduce symptoms and improve quality of life, both of which RT has been consistently shown to effectively accomplish (19, 20).

RT Challenges in PAC

PAC creates a trifecta of difficulty for effective treatment with traditional RT delivery strategies. First, is the significant difficulty of visualizing pancreatic tumors using traditional CT-based imaging strategies (21). The boundaries and locations of these tumors are exceptionally difficult to distinguish (18). Pancreas cancers are difficult to define on CT as they are hypo-attenuating with ill-defined borders. Even after contrast delivery, the Hounsfield unit difference between cancer and normal pancreatic tissue are nearly identical. Five to 14% of PACs are often iso-attenuating, blending imperceptibly with the normal pancreatic parenchyma. Second, is the location of pancreatic tumors close to exquisitely radiosensitive normal organs at risk for injury, specifically the small bowel and stomach. Critical is the fact that the small bowel is a "serial" organ at risk. Meaning if even a small portion of this organ is injured, the function of the entire organ is compromised. Clinical consequences of small bowel injury can be dire. The presence of the small bowel intimately associated with pancreatic tumors dramatically limits the ability to deposit meaningful doses of RT. Higher doses of RT have been associated with improvements in both OS and local control (22, 23). Yet, this must be done with exquisite caution for the small bowel in close proximity. Third, is the presence of highly variable, and unpredictable movement of both the primary pancreatic tumors and the adjacent normal organs. This trifecta is difficult to overcome, even with novel strategies using heavy ions, which are also susceptible to the unique challenges presented by PACs (24). Each of these components aggregate to make delivery of curative doses of RT to PACs exceedingly difficult to accomplish. Beyond just the total dose of RT, another currently controversial and challenging area is the optimal treatment volume that should be included. While historic strategies with SBRT included tumor only, there are recently published patterns of recurrence data that suggest the possibility of higher local and regional recurrences around the vasculature associated with focal SBRT including only the tumor (25, 26). Local recurrence along vascular structures, secondary to nearly ubiquitous peri-neural and peri-vascular invasion in PAC, remains a major concern. Historically, treatment volumes with fractionated RT have almost uniformly treated regional vascular structures to reduce this recurrence event. The high rates of regional nodal failure, secondary to peri-neural and peri-vascular spread, should be closely considered by radiation oncologists.

MR-Guided Radiation Therapy

MR-guided RT is a novel treatment technique that has emerged in the past 5 years and presents promise for a variety of solid tumors. There are two commercially available MRI Linear accelerators (MR-linac) systems including one by ViewRay (ViewRay Inc., Oakwood Village, Ohio) and a second by Elekta (Elekta AB, Stockholm, Sweden) (5). Several review articles have been published on this topic and a detailed overview of MR-guidance is beyond the scope of this article (27–29). In brief, rather than using a CT unit installed within a linear accelerator to localize the position of a tumor and normal organs prior to treatment delivery, a MR-linac combines an MRI device with a linear accelerator. Such a combination enables several capabilities that are uniquely helpful for the treatment of PAC. First, MR-guidance offers improved soft tissue contrast and thereby the ability to distinguish the boundaries of different types of soft tissue. This can include the location of a tumor, small bowel, stomach or vascular structures. Second, is that MR imaging on both commercially available MR linear accelerator devices is enabled when the beam is turned on and actually delivering RT. This results in the ability for normal organ movement to be tracked and monitored during the actual time of RT delivery. Such "real time" organ movement enables intra-treatment monitoring and will ultimately enable advanced dose tracking strategies. In other words, the precise radiation doses that were actually given to tumor and the normal structures will be understood during the actual treatment delivery. Real time imaging will enable entirely novel tracking approaches, previously unappreciated. Third, with MRgRT at each fraction a new treatment plan can be generated based on the actual MRI visualized anatomy. This is especially important for targets in areas were a large interfraction variation is expected like in PAC. Finally, in addition to anatomical imaging, functional and biological MR imaging can be routinely acquired, the meaning of which remains to be defined in most solid tumors. However, there is robust literature in the diagnostic space that many solid tumors exhibit early and clinically meaningful changes on MRI during a course of either chemotherapy or RT (30).

Rationale for MR-Guidance In PAC Over CT-Based Image Guidance

MR-guided therapy has recently presented itself as a highly appealing new option for patients with PAC. MR-guidance directly addresses several of the pivotal issues that have existed for decades with CT-based image guidance. First, is the ability to distinguish a tumor from normal pancreatic tissue. An example of a pancreatic tumor on CT simulation is seen in **Figure 1A**, despite a contrast enhanced CT, the ability to accurately identify the edges of many pancreatic tumors is nearly impossible. This is modestly improved with the use of a 1.5 Tesla MR-linac, even without IV contrast, as seen on the MR-linac image in **Figure 1B**. Additional work is needed to highlight the locations and conspicuity of pancreatic tumors. Highlighted in **Figure 2** is that many pancreatic tumors are located in such a position that the movement of small bowel can dramatically impact the dose of RT to those organs. An example of this is seen in the shaded region between **Figure 2**. The presence of bowel in this area changed significantly between fractions, and dosimetrically the recorded versus the observed bowel doses were significantly different. There is almost no question this normal organ movement has dramatically impacted RT dose in a variety of tumor sites, and especially in PAC.

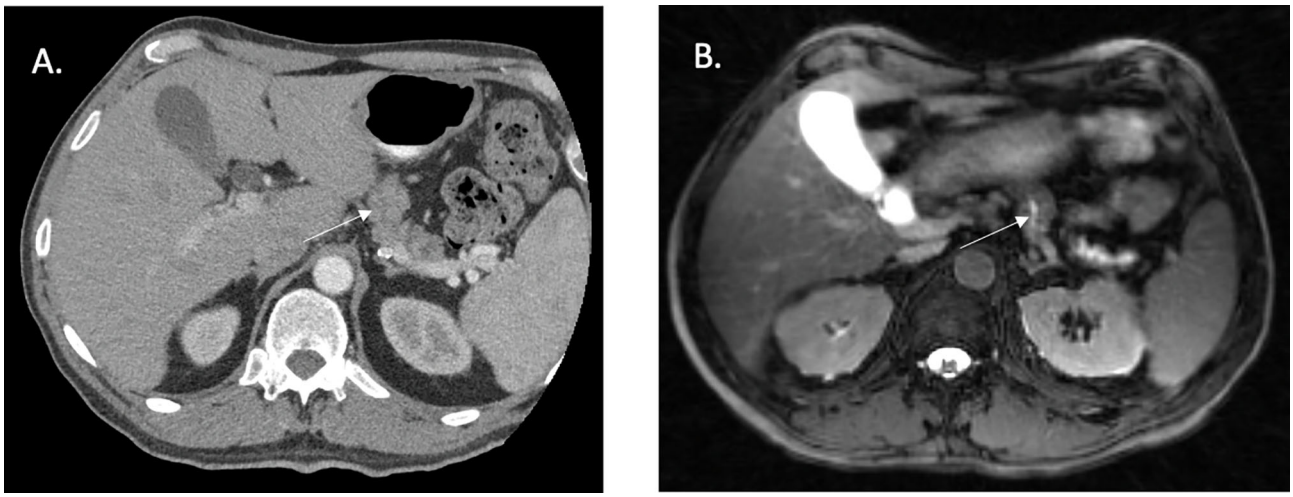

FIGURE 1 | CT simulation and fat suppressed T2/T1 MR images acquired from a 1.5 Tesla MR Linear Accelerator. **(A)** CT Simulation with contrast highlighting difficult to visualize pancreatic body primary tumor. **(B)** Slight improvement in visualization with images from 1.5 Tesla MRL, yet still difficult.

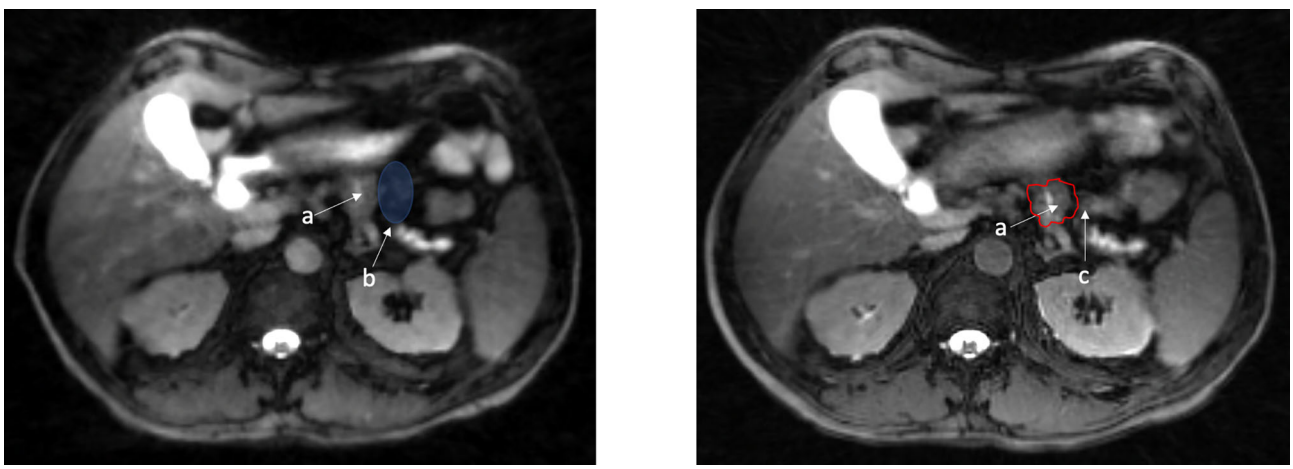

FIGURE 2 | Fat suppressed T2/T1 images acquired on a 1.5 Tesla MR Linac with illustration of a tumor in a close proximity to a potential space that can be occupied by moving small bowel. a. Small biopsy proven pancreatic body tumor. b. Potential space for small bowel to move. c. Example of small bowel movement in close proximity to gross tumor, max dose went from 26 Gy to 35 Gy (red 35 Gy).

Existing Series That Have Treated PAC Using MR Guidance

Despite MR-guidance being a relatively novel technological treatment strategy, there are several published retrospective series that have examined the ability of MR-guidance to improve the treatment of PAC. The majority of these published series have used the ViewRay MR-guided linear accelerator system (5), primarily because this has been FDA approved for a longer period of time than the Elekta MR-linac, and consequently accumulated more clinical data. Most of the currently published data is early feasibility work or small retrospective assessments.

One of the earliest clinical experiences examining the use of MR-guidance for the treatment of PAC was published in 2017. Bohoudi et al. describe stereotactic MR-guided adaptive radiation therapy, "SMART", for the treatment of PAC. In this study, the gross tumor was contoured and a 3 mm planning target volume (PTV) margin was applied. A total dose of 40 Gy in 5 fractions was prescribed, allowing 1% of the PTV to go to 50 Gy (9). This series also presented the feasibility of physicians adjusting the contours of the organs at risk (OAR's) within 3 cm of the PTV, rather than the entire abdominal cavity. Shortly after this publication, Henke et al. published their experience treating abdominal tumors that included a total of 3 patients with

recurrent PAC, along with 2 patients with primary PAC (10). This series also included patients treated for other abdominal tumors such as intra-hepatic cholangiocarcinoma, primary hepatocellular carcinoma, as well as metastatic disease. Conclusions from this series were that treatment with MR-guided RT was safe with low rates of toxicity. A relatively small number of patients with PAC, however, were represented in this series.

There have been three series published in the past two years including 25 patients or greater that have retrospectively assessed local control, toxicity, and OS associated with MR-guided RT in PAC (11, 12, 14). These series start to provide a window into clinical outcomes in patients with PAC treated with MR-guided RT. Important to consider is that MR-guidance is a highly novel treatment strategy, using unique and complex technology. Similar to many other complex oncologic interventions (such as robotic surgery) optimal outcomes will take time to emerge as techniques, methods, and skill sets using this technology develop and expand. While learning curves are well documented for some novel surgical techniques, they remain poorly studied and understood in advanced RT delivery (9, 31).

In the first of these series, Rudra et al. presented the results of 44 patients treated for inoperable PAC. This was a multi-institutional series that was one of the earliest to have aggregated data and presented outcomes focused specifically on high dose RT given with MR-guidance in PAC. Interestingly, OS was improved with the use of high dose (a BED_{10} dose greater than 70 Gy) MR-guided radiation in this series, 49% versus 30%, $p = 0.03$, with impressive rates of local control (over 75%) without any grade 3 toxicity. Given the retrospective nature of this series, there is the significant possibility of selection bias that must be considered when interpreting this data (11). Hassanzadeh et al. recently published their single institutional data examining patients treated with high dose ablative radiation for PAC (14). Again, high rates of local control, over 80%, with very acceptable rates of GI toxicity were demonstrated. Median OS rates in the series remained relatively similar at 15.7 months, which is similar to non-ablative, conventionally fractionated series from multi-institutional prospective trials. Significant work remains to understand how improved patient selection can contribute to improvements in OS.

Finally, Chuong et al. recently published a retrospective analysis of 35 patients treated using the ViewRay technology (12). They demonstrate excellent rates of local control and low reported rates of toxicity. Again, despite these seemingly strong outcomes, median OS and PFS were relatively similar, compared with other SABR pancreatic series. Important to note is the time point from which follow up data is being measured (from the end of RT versus time of diagnosis). **Table 1** summarizes the existing clinical series to have examined the treatment of PAC using MR-guidance.

ONGOING PROSPECTIVE TRIALS

Prospective research is desperately needed to examine novel RT applications in PAC. While retrospective series provide some framework, they should only be used as tools to design optimal prospective trials. Patient selection, and the potential for bias in retrospective studies is a confounder that can simply never be overcome. There are several ongoing trials that specifically focus on MR-guidance in PAC. The SMART trial is a well-known phase II trial examining the use of MR-guided radiation for locally advanced PAC and is currently accruing (NCT03621644). A total of 133 patients are planned for enrollment into this multi-institutional trial. The primary endpoint of this study is grade 3 or higher GI toxicity within 90 days of completion of RT. Given the relatively modest improvements in outcome over CT-based image guidance associated with MR-guided RT thus far, the SMART trial will ideally set the stage for future randomized trials providing a robust comparison between both CT and MR-guidance based RT modalities. An example of a patient treated on this clinical trial can be seen in **Figure 3**.

A second currently on-going study at Dana Farber Cancer Institute is a phase I/II study involving patients with either PAC, lung cancer, or renal cancer (NCT04115254). Primary endpoint for the phase I portion of the study is delivery success rate for SMART across multiple tumor types.

Finally the MOMENTUM study (NCT04075305) is an ongoing prospective registry that is currently collecting outcomes for patients treated with multiple solid tumors, including PAC using 1.5 Tesla MR-guidance. In this multi-institutional study, consisting of 7 centers with Elekta Unity linear accelerators, patients are being prospectively enrolled and followed for a multitude of outcomes. Patient-reported quality of life along with other detailed clinical outcomes data is being collected, including local recurrence and toxicity events. This will subsequently be used to inform prospective trials comparing MR-guided radiation with CT- based radiation.

CURRENT LOGISTICAL APPROACHES TO ONLINE ADAPTIVE MR BASED IMAGE GUIDANCE

A detailed discussion of methods, contouring strategies, and consensus approaches for implementation of online adaptive MR guidance for PAC is beyond the scope of this article. There are some helpful publications on PAC in general (32), not specific to MR-guidance (32). It should be recognized that online adaptive MR-guidance is a highly complex procedure that requires an engaged multi-disciplinary team including radiologists, radiation oncologists, physicists, therapists, and scheduling coordinators. The details of pancreatic tumor dosing and MR image guidance implementation has been the subject of recent publications. Specifically, tumor and normal organ delineation for PAC using MRI has been addressed in two recent review articles (33, 34). Dosing strategies, particularly those that may accomplish ablative dosing, have also been the subject of several recent review articles (35–37). Ablative dosing likely offers a higher probability of local control, and its implementation may be facilitated with online adaptive MR-guidance; but this remains to be conclusively determined. In

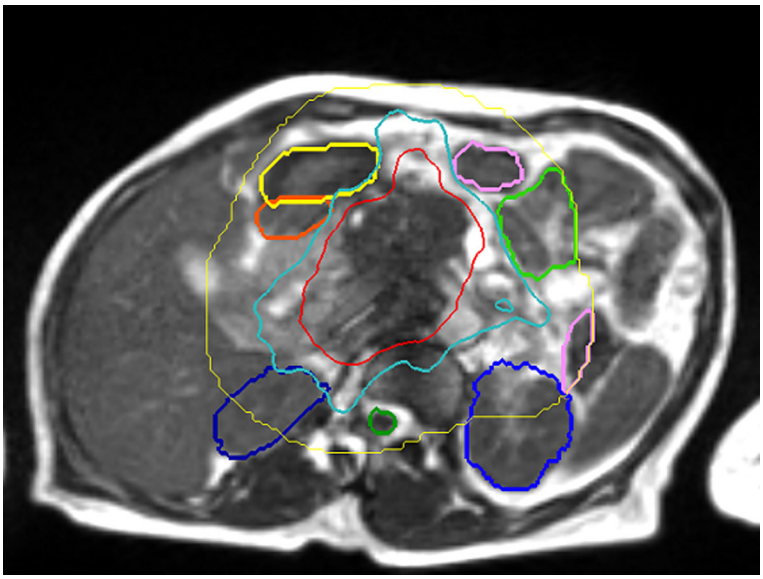

FIGURE 3 | View Ray 0.35 Tesla T2/T1 MR Guided RT. "SMART" patient (NCT03621644) – 50 Gy isodose in red, 33 Gy in cyan. Stomach in yellow, duodenum in orange, small bowel in green, kidney in blue (courtesy of Dr. Parag Parikh).

addition, device specific methods of online adaption that could also be considered have also been published (29). Finally, more practical methods for logistical delivery have been the subject of other recent publications and maybe of use for centers considering implementation of online adaptive MR guidance (13). Each of the clinical outcomes series presented in **Table 1** have associated methods that can be referenced for consideration regarding specific details of treatment strategies that have been

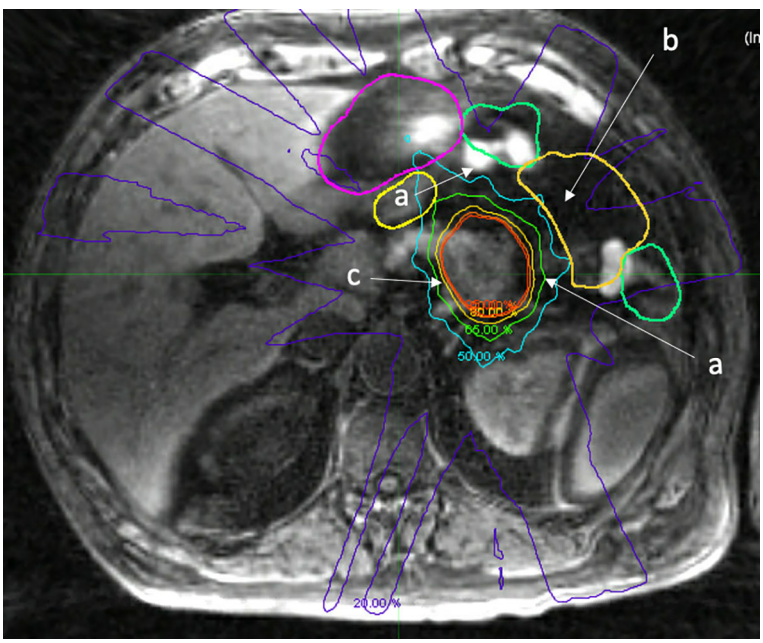

FIGURE 4 | Fat suppressed T1 image acquired on a 1.5 Tesla MR Linac immediately after treatment delivery highlighting normal organ movement during treatment that reflects uncertain dosimetric consequences. a. Movement of small bowel during treatment, differing from adapted contours (green, yellow). b. Void of small bowel that opened during treatment, actual RT dose to small bowel is likely not accurately measured, despite daily adaption. c. Isodose lines highlighting prescription dose with fall off.

applied. In addition, institutional selection criteria as to how patients are chosen for MR guidance methods in the upper abdomen have been previously published (13). In general, collaboration with experts, multi-disciplinary teams, and enrollment into clinical trials (with clear treatment protocols) is an optimal strategy for MR-guided treatment. At this time, the optimal strategy for MR guidance in PAC is still being determined, and clinical trials with detailed methodology is the best strategy for that determination.

FUTURE DIRECTIONS

The future of RT in PAC is at a critical precipice. Technology is rapidly evolving that will improve capabilities with RT. However, our understanding of how this technology should be optimally applied in PAC is contingent on prospective trial enrollment and detailed clinical outcomes publications. Traditional RT concepts, such as planning risk volumes (PRV's) accounting for normal organ movement or appropriate PTV expansions, are occasionally questioned for patients being treated with real time MR-guidance. **Figure 4** presents an example of how, despite optimal contour adaption before treatment, normal structures moved during treatment, and the dosimetric consequences of this movement are difficult to quantify and are poorly understood with current technology. Such movement may continue to justify including a PRV and PTV, unless it can be corrected or accounted for with exquisite accuracy in real-time. In theory, real-time treatment plan adaptation as the RT beam is delivering radiation dose could overcome this issue, however the computational time requirement associated with plan re-calculation times and imaging acquisition are currently prohibitive. That being said, it is only a matter of time before this computational power and ability is an immediate reality. This will very likely dramatically shorten treatment times and improve plan quality. There are many additional areas ripe for improvement in the therapeutic ratio in PAC. These include biological imaging-based response assessment (30), artificial intelligence-enabled real time contour adaptation (38), along with novel methods to account for accumulated RT dose to critical local normal structures. The future of highly personalized and adaptive RT in PAC is exceedingly promising, and radiation oncologists must lead the way *via* the education of our surgical and medical oncology colleagues. Novel RT treatment strategies need to be considered. Radiation oncologists must work closely with therapists, and physicists to optimize RT delivery and conduct ground-breaking clinical research. The systematic publication of outcomes is absolutely critical. Finally, randomized trials comparing MR-guidance to CT guidance would be helpful to quantify the magnitude of any benefit.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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REVIEW
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Online Magnetic Resonance-Guided Radiotherapy (oMRgRT) for Gynecological Cancers

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Radiation therapy (RT) is increasingly being used in gynecological cancer management. RT delivered with curative or palliative intent can be administered alone or combined with chemotherapy or surgery. Advanced treatment planning and delivery techniques such as intensity-modulated radiation therapy, including volumetric modulated arc therapy, and image-guided adaptive brachytherapy allow for highly conformal radiation dose delivery leading to improved tumor control rates and less treatment toxicity. Quality on-board imaging that provides accurate visualization of target and surrounding organs at risk is a critical feature of these advanced techniques. As soft tissue contrast resolution is superior with magnetic resonance imaging (MRI) compared to other imaging modalities, MRI has been used increasingly to delineate tumor from adjacent soft tissues and organs at risk from initial diagnosis to tumor response evaluation. Gynecological cancers often have poor contrast resolution compared to the surrounding tissues on computed tomography scan, and consequently the benefit of MRI is high. One example is in management of locally advanced cervix cancer where adaptive MRI guidance has been broadly implemented for adaptive brachytherapy. The role of MRI for external beam RT is also steadily increasing. MRI information is being used for treatment planning, predicting, and monitoring position shifts and accounting for tissue deformation and target regression during treatment. The recent clinical introduction of online MRI-guided radiation therapy (oMRgRT) could be the next step in high-precision RT. This technology provides a tool to take full advantage of MRI not only at the time of initial treatment planning but as well as for daily position verification and online plan adaptation. Cervical, endometrial, vaginal, and oligometastatic ovarian cancers are being treated on MRI linear accelerator systems throughout the world. This review summarizes the current state, early experience, ongoing trials, and future directions of oMRgRT in the management of gynecological cancers.

Keywords: gynecological cancers, MR-guided radiotherapy, MR Linac, SBRT, cervical cancer, online MR guided radiation therapy

INTRODUCTION

As early as 1990, magnetic resonance imaging (MRI) was described as a promising tool in management of gynecological cancers providing superior visualization of tumor and adjacent pelvic anatomy compared to other imaging modalities (1). In 1992 Russell published a review that highlighted the potential for MRI guidance to avoid marginal tumor misses in external beam radiation therapy (EBRT) of gynecologic cancer (2).

A decade later, the use of MRI was introduced in the brachytherapy (BT) planning process for patients with locally advanced cervical cancer (LACC) (3). MRI-guided (MRg) BT is based on an adaptive target concept that accounts for the topography of the primary tumor at diagnosis as well as the regression observed during EBRT (4). There is now a large collection of literature demonstrating that image-guided adaptive BT (IGABT) leads to better tumor control, increased survival, and decreased treatment toxicity (5–9). IGABT is supported by both the Groupe Européen de Curiethérapie European Society for Radiation Oncology as well as the American Brachytherapy Society and several guidelines have been published (3, 4, 10).

MRI is steadily gaining importance for diagnostic purposes and for optimizing the radiation treatment of gynecological malignancies (11). It has become a key component of initial disease staging for cervix cancer (12), and MRI findings are now integrated in the International Federation of Gynecology and Obstetrics (FIGO) cervical cancer staging system. MRI has been adopted as the imaging modality of choice for the management of patients with cervical cancer due to superior soft tissue contrast compared to computed tomography (CT). This allows for better visualization of the pelvic and abdominal organs and better distinguishing tumor from adjacent healthy tissues. Sequential MRIs during EBRT can capture inter- and intra-fraction motion, deformation of the tumor and the surrounding organs, and tumor regression over time (13, 14).

The integration of an MRI in a linear accelerator (MR Linac) treatment unit (Unity, Elekta, Sweden; MRIdian, ViewRay, Cleveland, OH, USA) constitutes a real breakthrough for the management of gynecological malignancies, allowing physicians to perform online adaptive radiation therapy (ART) based on the anatomy of the day and to monitor anatomical changes during a treatment course. Utilizing ART, new strategies are being developed to increase EBRT conformality and further individualize treatment plans. Treating gynecological malignancies with an online MRg radiation therapy (oMRgRT) approach has the potential to reduce treatment toxicity and optimize tumor control, which would be consistent with IGABT results.

Patient selection depends on patient characteristics and disease characteristics. Patients could be physically incompatible for oMRgRT based on the presence of non-MRI compatible cardiac implantable electronic device, or any other type of metallic implant/foreign bodies or clinically incompatible, for example, patients suffering from claustrophobia, severe anxiety, pain preventing them from being able to hold the same position for a long time on the treatment table (the whole replanning, treatment delivery process might be up to 60 min). In terms of disease characteristic, there is a large spectrum of gynecological cancers that might benefit from oMRgRT. In the curative treatment of cervical cancer, oMRgRT may be utilized for elective EBRT nodal boosts and primary tumor boosts if first-line BT is not feasible. Patients with gynecologic cancers who might also benefit from oMRgRT include those with locoregional recurrences after surgery and those with oligometastatic who are no longer responding to systemic therapy or are not candidates for systemic therapy due to the presence of comorbidities (15). For the latter group, oMRg stereotactic body radiation therapy (SBRT) could be applied to both nodal and soft tissue metastasis to achieve target tumor control with limited morbidity. SBRT of oligometastatic disease has been reported to increase survival while preserving quality of life (16).

In this manuscript we review early clinical applications of oMRgRT and its use for various gynecologic tumor sites and with different treatment intents and reflect on current hypotheses supporting the use of oMRgRT in gynecologic cancers.

TREATMENT OF LOCALLY ADVANCED CERVICAL CANCER

Definitive treatment of LACC consists of EBRT to the primary tumor, the entire cervix and uterus, the parametria, the upper vagina, and draining lymphatic regions along with nodal boosts to positive nodes usually combined with chemotherapy (mostly weekly cisplatin). Elective paraaortic (PAO) nodal irradiation may be indicated in some patients. It is standard of care to deliver a BT boost to the residual primary tumor after EBRT. BT and EBRT both benefit from MRI guidance, but in different ways.

With modern radiation therapy (RT), daily verification for target positioning has improved significantly. Since the 1990s, EBRT has evolved from the use of Port films and skin marks to the use of cone beam CT (CBCT) with or without fiducial markers for more precise targeting of soft tissue lesions. Daily on-board image guidance has become standard of care, but the suboptimal soft tissue contrast provided by CBCT makes it challenging to distinguish soft tissue tumor from surrounding normal tissues, particularly in the pelvis.

MRI provides superior soft tissue contrast compared to CT. As opposed to CBCT, there is no additional ionizing radiation exposure when MRI is used for on-board daily imaging. Ultrasound imaging can also provide a low-cost, non-ionizing radiation verification tool in LACC radiotherapy (18) and can be linked with treatment delivery. However, whilst the uterus, cervix, and bladder can be identified reliably, other OARs are not easily visualized.

MRI is already integrated into the radiation treatment planning pathway for LACC. In addition to providing better soft tissue resolution, MRI has the advantage of allowing depiction of disease extent in more than one plane (17). The possibility to perform image acquisition in two orthogonal planes along the tumor axis provides important information on disease extent for cervical cancer staging.

The BT literature has demonstrated the pivotal role of MRI in improving delineation of the high-risk clinical target volume

(HR-CTV) (7) leading to better tumor control and reduced treatment toxicity (7–9).

Adaptive Radiation Therapy in the Management of LACC

In the management of patients diagnosed with LACC, it is well known that the primary tumor exhibits large inter fraction motion due to day-to-day changes in the volume of the surrounding pelvic organs (mainly bladder, rectum, and other parts of the bowel) seen during the delivery of pelvic EBRT. Haripotepornkul et al. (18) calculated the inter-fractional movement of the cervix during intensity-modulated radiation therapy (IMRT) in the lateral, vertical, and anterior-posterior directions as 1.9, 4.1, and 4.2 mm, respectively. The simplest strategy used to deal with target inter-fraction and intra-fraction motion has been to add a generous planning target volume (PTV) margin of 1.5–2.0 cm to the target volume. This expanded security margin is necessary to ensure full dose to the target, but the cost of this approach is that a large part of the surrounding normal organs receives the same dose of radiation than the target volume.

Treating cervical cancer with ART can enhance precision during EBRT by correcting for the inter-fraction motion, thereby reducing PTV margins and the volume of non-target tissues that receive high-dose RT. Early exploratory studies on the use of oMRgRT demonstrated that daily MRI permits adaptation of EBRT plans to daily tumor and organs at risk (OAR) positions (14). The use of ART potentially leads to a considerable reduction in OAR dose, by facilitating improved accuracy of treatment delivery and enabling margin reduction.

A more recent comparative study of various ART techniques using CBCT with standard margins, reduced margins, and oMRgRT demonstrated that incremental dosimetric gains can be made in OAR sparing through the use of more advanced technology (19).

Another ART concept, only achievable with MR Linacs, challenges the convention of including the whole uterus in HR-CTV target volume. Contemporary consensus contouring guidelines for IMRT for cervical cancer advise including the whole uterus (20). These guidelines were written based on the limited ability of CT to identify intrauterine tumor extension. The safest way to deal with this uncertainty was to include the whole uterus in the initial target volume and to add a large margin on this volume to account for inter-fraction fundus motion. The ability of MRI to distinguish tumor from normal uterus introduces the possibility of targeting the tumor only rather than the tumor, cervix, and the whole uterus. A preliminary modeling suggests this is a feasible approach that could further reduce OAR dose (19). Kozak published a single institution retrospective study of 53 patients with LACC treated per institution policy with less than whole uterus irradiation volume and showed comparable locoregional control and reduced bowel V40 and D200cc when the outcomes from the cohort studies were compared to historical series (21). These preliminary data should not lead to broad clinical implementation but rather be seen as provocative results that deserve being tested in a larger multicenter international prospective study to confirm the safety of this approach.

Daily adaptive planning can significantly reduce treatment margins sparing surrounding OAR without compromising target coverage; however, these techniques are complicated, time-consuming, and resource intensive. Based on CTV-PTV margins of 3–5 mm, an online adaptive planning strategy can reduce dose to rectal V4000cGy by 36–47%, dose to bladder V4000cGy by 43–59%, and dose to bowel V4000cGy by 13–30% compared to a non-adaptive approach (19). As oMRgRT and auto-segmentation technology continue to improve, the burden of daily adaptive planning may be significantly reduced. Until these gains are realized, daily adaptive planning for cervix cancer may be impractical. However, a practical approach to mitigate the large treatment margins necessary for accounting for inter-fraction motion is to utilize a plan-of-the-day (POTD) technique (22).

The POTD technique utilizes an individualized IMRT plan library that is selected based on the patient's internal anatomy at the time of daily setup. POTD technique has the potential to reduce the treatment margins compared to conventional treatments, but it has a more manageable workload and faster treatment time compared to daily ART. Buschmann et al. published their experience with 16 patients using a volumetric modulated arc therapy (VMAT) plan library for bladder full, bladder empty, and a motion robust backup plan, where plan selection is based upon daily setup CBCT. MR Linac systems could use a similar methodology but have the added benefit of creating the plan library as needed on fractions that do not have a suitable match in the current library for the patient, resulting in an adapted plan for the day and an additional entry into the plan library (**Figure 1**). Additionally, the improved MRI image quality compared to CBCT image will ease plan selection for those fractions where a predefined plan will suffice.

Although using oMRgRT for LACC has been seen as one of the key examples for using the ART approach with MR Linacs (given the good MRI visualization and large inter-fraction motion), to date clinical implementation of this treatment is limited. The main drawback of the currently available MR Linacs systems is the limited treatment field size [feet/head extent: 22 cm (Unity/Elekta), 24.1 cm (MRIdian/ViewRay Cleveland OH)], which especially hampers treatments that include elective treatment or nodal boosts, which could extend up to PAO nodes. Technically, a multiple isocenter approach may solve this; however, long treatment times, added treatment planning complexity (which might be challenging to safely integrate in an online planning workflow), and the risk of irradiating the same volume twice (especially the bowel) are to be considered in implementing this technique. Solutions including VMAT and tomotherapy approaches might provide additional gain.

Hypofractionation approaches could also be a practical solution to make oMRgRT workable. As it has been shown for other pelvic tumors (23, 24), the need for strict adherence to prescriptions of 1.8–2 Gy per fraction when treating the central pelvis plus nodes can be challenged. Hypofractionation used to be considered a safe approach only for small-volume targets, but there is growing acceptance that larger volumes can be treated similarly, provided doses to the more sensitive OAR such as

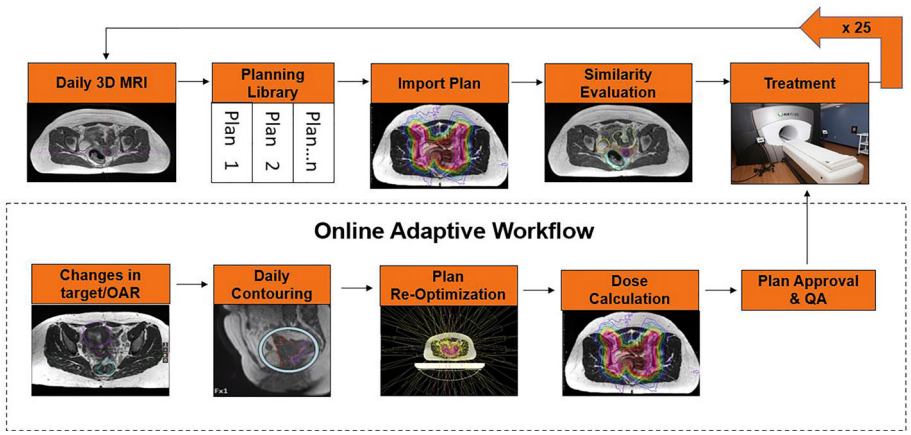

FIGURE 1 | POTD approach for oMRgRT for cervical cancer.

bowel can be minimized. Studies exploiting the benefits of integrated MR Linacs for enhanced target and OAR visualization and online adaptation to treat LACC with hypofractionated schedules are in progress (25) and if successful will facilitate the wider adoption of daily replanning for cervical cancer.

Potential Gain of oMRgRT When Brachytherapy Is Not Feasible

oMRgRT can also be used to substitute the final BT boost in selected cases (e.g., patients with comorbidities limiting their capacity to undergo invasive procedures, BT implantation technically not feasible). The first experience with this novel treatment approach has been published (26, 27). Due to the limited dimensions, delineated volumes, and number of fractions, this treatment option is easier to implement than treatment of longer EBRT fields. Compared to BT, however, with oMRgRT the target dose will be limited if isotoxic OAR constraints are used (27, 28). Focus on the OAR constraints is important, which is exemplified by the high toxicity reported in one study (29) in which relatively high OAR doses were allowed. Strictly using the current recommended BT OAR dose constraints for MR Linac SBRT treatments may be a good starting point to prevent high toxicity. In such an approach the OAR dose is driving the choices in treatment planning, and it can be expected that daily online re-planning with MR Linacs may deliver less dose to the targets compared to BT, but more target dose can be expected compared to CBCT-guided treatments (26). It was demonstrated in the BT literature that adhering to high-dose levels to the HR-CTV is critical to obtain local control (LC) (30, 31). As current studies show that the target dose is reduced using MR Linac treatments compared to BT (26, 29), and the efficiency of SBRT is still considered limited (32), BT remains the superior treatment option. A SEER review published by Eiffel has clearly demonstrated that the use of BT in the management of patients with LACC is associated with improved survival (33). MR Linac treatments should not be considered a replacement for BT, but it could be an option in selected cases where BT is not possible and, in these cases, might be preferable over CBCT-guided SBRT. A typical example is provided in case 1 below.

The availability of an MR Linac treatment unit in the Radiation Oncology clinic has the additional benefit of providing easy access to MRI datasets with applicators in place to aid in MRg BT planning. This can greatly simplify the logistics of doing IGABT for many institutions who until now had relied on the limited availability of MRI scanners in the diagnostic radiology department (34). **Figure 2** is an example of a BT MRI study obtained using a 0.35 Tesla system. After immobilizing the applicators with a clamp or other MR-compatible device, the patient is transferred to the MR Linac room on an MR-compatible stretcher.

Functional Imaging and Dose Painting

An additional appeal of integrated MR Linacs is the ability to perform serial functional imaging through the course of EBRT. The information obtained might be used to guide decisions on boosting poorly responding targets or as a prognostic tool to define the need for additional therapies. Diffusion weighted imaging (DWI), where random Brownian motion of water within tissues is detected, is currently used to determine malignant from benign tumors by measuring apparent diffusion coefficient (ADC) values. Malignant tumors exhibit a low ADC value and in combination with T2WI are highly sensitive in delineating tumor from surrounding tissues. Studies have demonstrated that serial ADC measurements during the treatment course can be used as an independent prognostic factor for treatment response, where increase in ADC values during treatment represents tumor response, thus aiding in identification of good responders (35, 36). DWI also demonstrates heterogeneity within the tumor, indicating areas of resistant clones as well as regression. With automated contouring, thresholds can be set for ADC values, and these areas could be targeted with a "dose painting" strategy—a concept whereby different doses can be delivered within the tumor.

Feasibility of using diagnostic DWI on the MR Linacs has been demonstrated, but reproducibility across systems and

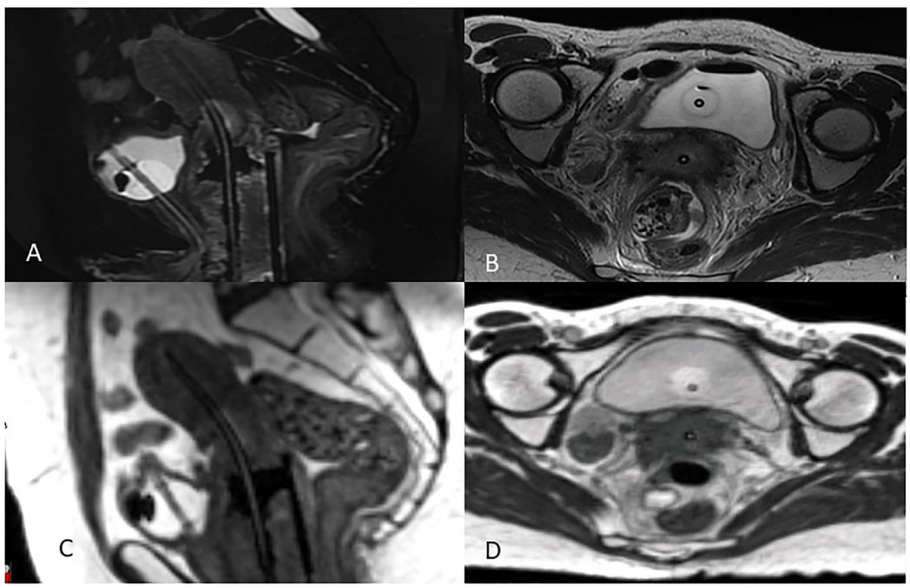

FIGURE 2 | MRg Brachytherapy 3T Diagnostic MRI **(A)** Sagittal and **(B)** axial views compared to 0.35T MRIdian MRI **(C)** Sagittal **(D)** axial views.

institutions is challenging due to inconsistent hardware and acquisition methods. With MR Linac institutions working in collaboration, work can be undertaken to identify appropriate sequences that can be applied across all machines, which will allow for reliability as well as repeatability. This collaborative approach, fostered in cervical cancer through the EMBRACE network, has been replicated in a sub study, iEMBRACE, which is currently investigating the use of serial functional imaging on diagnostic platforms as a prognostic tool in cervical cancer. The first step to standardize measurements across institutions has been successfully implemented.

Current research, using sequences acquired on MR Linac, will investigate the potential of other functional MRI sequences to measure tumor and normal tissue response (e.g., dynamic contrast enhanced (DCE) MRI).

TREATMENT OF INOPERABLE ENDOMETRIAL AND RECURRENT GYNECOLOGICAL CANCER

Inoperable Endometrial Cancer

The standard treatment of localized endometrial cancer is surgery consisting of hysterectomy with bilateral salpingo-oophorectomy with or without regional lymph node dissection or sentinel lymph node mapping. This treatment may need to be followed by radiotherapy and/or systemic treatment depending on histopathologic risk factors. A minority of patients are unable to undergo surgery due to advanced age, poor performance status, or medical contraindications to anesthesia. These patients can be treated with definitive radiotherapy consisting of EBRT and/or BT. Depending on the tumor stage, disease control and long-term survival are achievable (37–40). In a cohort of 1,322 patients with endometrial cancer treated with radiotherapy alone (EBRT and/or BT) for various reasons, the disease-specific survival at 5 years was 78.5%. Reported severe late morbidity (≥ grade 3) was as low as 3.7% for the combined treatment approach (40). In a smaller retrospective study, 74 patients with stage I and II endometrial cancer have been investigated. The majority of patients received a combination of pelvic EBRT and BT with curative intent, resulting in a 3-year progression-free survival of 68% with a median interval of 43.5 months (38). BT alone has been applied with curative intent, with excellent LC up to 100% in well-selected patients (41, 42).

For patients not able to undergo surgery and/or BT, the functionality of MR Linacs might have potential for improving EBRT. The suggested benefit of an oMRgRT and replanning over standard EBRT is the opportunity to truly adapt the treatment plan to the anatomy of the day. Variations in uterine position based on bladder or rectal filling can be visualized and accommodated rather than having multiple plans created ahead of time from which to choose the most appropriate plan of the day. As described earlier, for patients with LACC, the MR Linac treatment fields are limited in a cranial-caudal direction. The current available field lengths (Unity/Elekta: 22 cm; MRIdian/ViewRay: 24.1 cm) can be too limited for pelvic fields in tall patients, or if PAO elective radiotherapy is indicated. However, MR Linacs provide the possibility for boosting the uterus and any metastatic nodes in addition to elective EBRT when a BT boost to the uterus is not feasible. Daily MRI guidance and replanning allow for better targeting of the dose to the uterine cavity and extensions of the disease into the uterine wall and/or cervix while adapting for the variable positions of the

sigmoid, small bowel, and bladder. Though the achievable target doses are not expected to be as high as with BT, a meaningful boost may be achieved dependent on volume and extensions of disease remaining after external beam. To date, there are no clinical cases/studies published reporting the early experience with this new treatment option, and therefore the potential gains remain theoretical.

Vaginal Vault Recurrences

Vaginal recurrences can occur after treatment of cervical, endometrial, and vaginal cancers. Depending on the initial treatment of the primary tumor, treatment for recurrent disease may consist of surgery, chemotherapy, and/or RT (43, 44). When surgery is not an option, EBRT, BT, or both may be needed. The dose and fractionation will depend on the prior treatment. SBRT and especially IGBT show encouraging results (45). BT offers the most definitive boost treatment, and high LC rates can be achieved (45, 46). In an overview of 28 patients described by Fokdal et al., the 2 years LC rate was 92% (46). However, not all recurrences are amenable to BT salvage. An example may be a rectovaginal septum recurrence in close proximity to the rectal wall. In these complex situations, interstitial implants might be needed but are often not achievable, and the risk of fistula formation after treatment is high. In these situations, an external beam boost using the advantage of oMRgRT adjusting the plan to the daily anatomy with relatively homogeneous dose distributions may provide a good alternative. Utilizing isotoxic treatment planning for each fraction, tailoring dose away from the uninvolved rectum and other surrounding organs, and the avoidance of extremely high doses around the individual interstitial brachytherapy needles might result in less normal organ damage (including necrosis). Case example 2 demonstrates the first clinical experience with such a situation.

Pelvic, Abdomen, Abdominal Wall Recurrences

Single or oligo recurrences of gynecological cancers at other locations in the abdomen (pelvic wall, abdominal wall, lymph node recurrences, and other soft tissue lesions) can be treated with surgery and/or radiotherapy to achieve long-term LC (47). Salvage surgery is not always possible, either due to unfavorable locations and/or anatomically challenging situations in case of repeated surgical interventions or patients unfit for surgery (48). Salvage irradiation can be used as an alternative to treat these recurrences (49). SBRT has curative potential in patients with recurrent gynecological malignancies (50). In a cohort of 30 patients treated with SBRT for metastases in the pelvis and/or the PAO region, 9 of 35 lesions treated with SBRT failed locally (26%), resulting in LC rates of 80 and 73% at 1 and 2 years and a 5-year survival of 42%. These results are promising in the setting of metastatic disease but also show that improving LC might have additional potential. In these situations, MRI guidance and online replanning might offer dosimetric gain, especially when SBRT, with the typical sharp dose gradients, is planned but highly mobile sensible OARs are in close proximity and vulnerable to injury. For first clinical experience, see *Case Example 2*.

TREATMENT OF OLIGOMETASTASIS/ METASTASIS OF ANY GYNECOLOGIC SITES

oMRgRT for the Management of Oligometastatic Disease

The concept of oligometastatic disease was first introduced in 1995 by Hellman and Weiselbaum (51), with the description of an intermediate state of metastasized disease between a locally confined and a widespread metastatic disease. The oligometastatic state was recently defined by an ESTRO-ASTRO consensus as one to five metastatic lesions where all metastatic sites must be safely accessible for curative intent treatment, with a controlled primary tumor being optional (52, 53). Early clinical studies showed an improvement in progression-free survival or overall survival (54–56) by the addition of metastases-directed therapy to standard-of-care systemic therapy in solid tumors. Today, this approach is supported by a large number of high-quality studies (57–59) and has rapidly gained attention in the field of radiation oncology as the proportion of patients receiving metastasis-directed therapy is constantly growing (60).

Several recent technology developments have facilitated the applicability of this concept: first, improved diagnostic imaging (e.g., PET-CT) enables an early detection of low disease burden. With the clinical implementation of high-precision local-ablative treatments such as SBRT, high LC rates with usually low toxicity can be achieved, while in parallel more effective systemic treatments have led to a prolonged overall survival of metastatic patients. Finally, we have improved the biological and clinical understanding of tumor biology; today genetic, molecular, or cellular analyses can help to tailor cancer treatments in the setting of precision medicine (61, 62).

SBRT is a local treatment modality that can be applied in few treatment sessions, allows simultaneous treatment of multiple targets at distant sites, and can be integrated into multimodality treatment regimen with minimal interference with systemic treatment delivery. However, current image-guided RT methods using on-board CBCT are limited due to the reduced soft-tissue contrast. It remains difficult to distinguish tumor from normal tissues, with the consequence that dose escalation strategies are not feasible in all anatomic regions, or generous target volume margins are applied to compensate for uncertainties in dose delivery and target coverage (61, 63). In this context, the application of oMRgRT marks the beginning of a new era. It allows direct visualization of the tumor and healthy tissues and provides real-time imaging during dose delivery. In addition, online ART allow to optimize dose escalation, while reducing dose to surrounding OAR on a daily basis. This technology offers the potential to further push the limits of local ablative treatments in the setting of oligometastatic disease.

oMRgRT in the Management of Oligometastatic Lymph Node Metastases From Gynecologic Malignancies

Isolated lymph node metastases from gynecologic malignancies are considered a good indication for SBRT, as they usually occur

within the pelvis or the PAO lymph node region (64, 65). SBRT can be applied in the setting of limited oligometastatic disease, with the aim of postponing or enhancing systemic therapies, or as an alternative to surgical resection (66). Patients are usually asymptomatic, as the disease burden is extremely low. In this setting, SBRT offers excellent tumor control rates with a low toxicity profile due to the small target volumes (67–69).

Obviously, this approach carries the risk of out-of-field local progression in other regional lymph nodes, which happens in 10–30% of patients (67). Locoregional progression could be prevented by using larger EBRT fields, which on the other hand might be limited due to overlapping volumes or treatment fields with previous radiotherapy areas and lead to higher morbidity rates (67). The fact that the risk of locoregional failure is low supports the rationale for the use of more limited field in patients with oligometastatic disease. A permanent remission can also be achieved by the iterative application of local interventions (70). Further studies are needed to identify specific biomarkers for accurate patient selection of true oligometastatic disease and determine the optimal way to integrate and sequence SBRT in multimodal treatment approach (53).

The effectiveness of SBRT on LC is clearly associated with a dose-response correlation; higher biologically equivalent dose (BED) leads to better tumor control (71, 72). For lymph node metastases, 5-year LC rates of uterine, cervical, and ovarian cancer range from 70 to 97%, and favorable disease-free survival and overall survival are reported in retrospective series (64, 68, 70, 72–77). Lymph node metastases of gynecologic malignancies are often located in the pelvis or abdomen, where conventional SBRT using CBCT image guidance yields relatively poor soft tissue contrast. Hence, it may be difficult to deliver a sufficient dose to the tumor because it is challenging to identify the interface between the lymph node metastasis and surrounding healthy tissues (e.g., bowel), even if a steep dose gradient can be achieved with SBRT. In these clinical scenarios, oMRgRT offers significant advantages, as it allows a direct visualization of the metastases on MRI and enables margin reduction or dose escalation strategies by using online ART and automated gating systems (78). Comprehensive documentation of treatment outcomes of the first successfully delivered treatments will confirm whether or not it will translate into a clinical benefit. There is no data from large series available yet.

Early experiences with MRg SBRT of lymph node oligometastases of other primary tumors show promising results (61, 65). A dosimetric comparison of the dose coverage and compliance to dose constraints of an MR Linac workflow with a CBCT workflow in lymph node SBRT showed a lower number of unplanned violations of high-dose criteria using the adaptive MRg treatment planning at comparable target dose coverage (79). oMRgRT can provide correction for inter-fraction setup uncertainties, changes in size and shape of the tumor, as well as the anatomical alignment to OAR. To fulfill this task, several plan adaptation strategies are available on MR Linacs (80), which vary from simple weight optimization or multileaf collimator shifts to advanced full online adaptive replanning where a completely new treatment plan is generated. The goal of daily plan adaptation can be to improve target coverage, OAR sparing, or both (78). A recent study of Winkel et al. (80) showed that in patients with oligometastatic lymph node metastases, the most advanced optimization method, using a full online replanning, performs as good as pre-treatment planning, yields the most favorable dosimetric values, and can be performed within a reasonable timeframe.

oMRgRT for the Management of Oligometastatic Distant Metastases From Gynecologic Malignancies

A small subgroup of patients diagnosed with oligometastatic distant disease may benefit from local metastases-directed therapy, even if treatment options have traditionally been limited to systemic therapy with palliative intent in this clinical setting (68). Lazzari reported on the outcome of SBRT in oligometastatic ovarian cancer (74). SBRT in oligorecurrent or oligoprogressive disease in intensively pretreated patients (median of three prior systemic therapy regimens) showed excellent LC rates without any grade 3 or 4 acute or late toxicity. The median systemic treatment-free interval after SBRT was 7.4 months, and more than one-third of patients were still disease-free at 1 year after SBRT. In this context, SBRT was able to postpone systemic therapy and allowed "drug holidays" in a heavily pretreated group of patients. Since the failure pattern was predominantly out of field (75%), multiple SBRT courses were used as a salvage option in case of subsequent recurrence.

In the treatment of distant metastases (liver, lung, bone, soft tissue), higher BED correlates with better LC rates (81, 82). Kunos et al. (81) achieved an LC rate of 100% in metastatic gynecologic cancers with a prescription dose of 24 Gy in three fractions (70% isodose), and Mesko et al. (82) reported an LC rate of 83% after applying a median dose of 40 Gy in five fractions. In contrast, Lazzari et al. (74) reported an LC rate of only 70% for distant metastases after SBRT with 24 Gy in three fractions, while lymph node metastases reached higher LC rates of 81% with the same fractionation. A large retrospective multicenter analysis of SBRT of 449 ovarian cancer lesions (76) found that an age of ≤60 years, a PTV size of ≤18 cm3, lymph node disease, and a BED ($\alpha/\beta 10$) of >70 Gy were independent predictive factors of complete response on multivariate analysis. SBRT is technically feasible in all anatomic regions. The fractionation and prescription dose vary widely based on tumor-related parameters (lesion size, proximity to vulnerable OAR, organ and tumor motion) and if the target lies in a previously irradiated field. Breathing motion and changes in the filling status of surrounding OAR can present a challenge (83). oMRgRT can improve the feasibility of delivering SBRT for oligometastatic distant disease, enabling dose escalation. In addition to the advantages of online ART, MR Linacs allow for a direct visualization of the target during treatment delivery. The 0.35T MR Linacs can automatically gate the beam by using real-time anatomy structure tracking at a rate of eight images per second (84). This eliminates the need for invasive implantation of fiducial markers and the addition of an ITV to account for intra-fractional motion, leading to reduced healthy surrounding tissue irradiation (85, 86).

Appropriate patient selection is key for success. The treatment of oligometastatic distant disease with a limited number of lesions can represent a spectrum of clinical scenarios, which are associated with different prognoses and might require different treatment strategies. In a recently published ESTRO-EORTC consensus, an attempt was made to characterize and classify the different possible stages of oligometastatic disease (53). The classification differentiates between a true oligometastatic disease and an induced oligometastatic condition, where patients had a prior history of polymetastatic disease. Furthermore, oligorecurrence, oligoprogression, and oligopersistence were classified, considering whether the oligometastatic disease was diagnosed during a treatment-free interval or under active systemic therapy. However, to date no biomarkers are available to identify patients with true oligometastatic disease, and the sole presence of limited disease is sometimes difficult to interpret (53). In a retrospective analysis, patients with limited disease burden of ovarian cancer (stage I-II, no residual tumor after first surgery, fewer previous systemic therapies, ≤2 lesions treated, time since last chemotherapy ≥7 months) had a better outcome than patients undergoing SBRT after failure of multiple lines of chemotherapy or in case of induced oligometastatic disease (74). These patients may not have been in a truly oligometastatic state at the time of SBRT. Therefore, further studies are needed to establish adequate selection criteria and to define the role of SBRT in the multidisciplinary treatment strategy of oligometastatic distant metastases and its influence on survival outcome.

oMRgRT for the Management of Oligometastatic Paraaortic Relapse

A minority of patients develop oligometastatic relapse in the PAO region after curative surgery or pelvic (chemo)radiation for primary gynecological cancers (especially cervix or endometrial origin). For these patients, PAO irradiation with or without systemic treatment can be offered as salvage option (87). PAO irradiation can be applied as regional elective treatment including simultaneously integrated boosts (Sib) to macroscopic nodal metastases or as localized approach (especially SBRT) for macroscopic disease alone (88). Dose levels needed to achieve control are 45–50 Gy in 25–28 fractions for elective volume and a dose range of 50–65 Gy for macroscopic disease (88). The proximity of these nodes to the bowel is a dose-limiting factor. Severe duodenal morbidity was reported after PAO irradiation using Sib to nodes in the upper abdomen (87, 89). MR Linacs might be the technology of choice in these situations as daily visualization of the anatomy together with the possibility for online ART allows for a broader therapeutic window with better tailoring of the dose to the metastatic nodes and away from the surrounding bowel (duodenum) loops (see *Case Example 3*).

CLINICAL CASES

Case Example 1: Primary Cervix Cancer; MR Linac Boost to Primary Tumor (Figure 3)

A 54-year-old patient with FIGO stage IVA cervical cancer

Primary tumor infiltrated the distal parametrial tissue, rectovaginal septum, upper vagina, rectal wall, and bladder mucosa and was associated with bilateral hydronephrosis. Patient's history included brainstem infarction with persistent hemiplegia and need for anticoagulation. Multidisciplinary recommendation was to offer a curative treatment. EBRT was delivered with VMAT (45 Gy in 25 fractions to tumor and lymphatic drainage) with bilateral Sib (2.35 Gy per fraction) for two positive obturator nodes. Concurrent chemotherapy could not be administered due to severely impaired kidney function and comorbidity. Initial plan included a BT boost (four HDR fractions, aiming at a total D90 HR-CTV of 90 Gy EQD2α/β=10).

After 32.4 Gy of EBRT, repeated MRI showed only minor tumor regression and persistent tumor invasion in the rectum and bladder. Tumor volume was reduced from 174 to 118 mm3, and largest dimension was still significant (from 93 to 80 mm). Therefore, BT was no longer considered feasible, and a boost was delivered using oMRgRT instead.

The boost was delivered in four IMRT fractions using an 11-field beam arrangement. Planning was done using an isotoxic approach with priority given to OAR dose constraints over target coverage. The HR-CTV and relevant OAR were re-contoured before each fraction using the daily MRI and online ART was performed.

The pelvic EBRT dose (45 Gy or 44.25 Gy, EQD2α/β=10) was added to the dose from the four online adaptive plans to calculate the cumulative dose, which was as follows: D90 HR-CTV: 76.4Gy EQD2α/β=10 (i.e., 6.0 Gy, or 8.1 Gy, EQD2α/β=10 per fraction), and OAR doses were bladder D2cc: 90.9, rectum D2cc: 70.0, sigmoid D2cc: 47.3, and bowel D2cc: 74.9 Gy EQD2α/β=3. Although D90 HR-CTV was below the recommended dose (D90 ≥ 90 Gy EQD2α/β=10), using this stereotactic planning approach at least part of the HR-CTV received this dose with V90GyEQD2α/β=10 = 19%, and V85GyEQD2α/β=10 = 64%. Our institution approach (UMCU) for CBCT Linacs would have allowed for a total D90 HR-CTV of 70 Gy EQD2α/β=10 using VMAT with uniform target dose distribution.

Treatment was well tolerated without unexpected early toxicity. First follow-up including MRI-based response evaluation will be performed 3 months after treatment.

Case Example 2

A 68-years-old patient diagnosed with FIGO stage IIIB grade 2 endometrial cancer, treated with laparoscopic hysterectomy and bilateral salpingo-oophorectomy. On the treatment planning CT scan and MRI, recurrent tumor was detected in the vaginal vault, and additionally a second lesion was seen in the anterior abdominal wall (most likely a laparoscopic port site recurrence). Biopsy of both lesions confirmed metastases from endometrial cancer. Patient was considered ineligible for additional surgery due to comorbidities including severe obesity. Definitive radiotherapy was planned, consisting of sequentially oMRgRT SBRT for the abdominal wall metastasis (35 Gy in five fractions), followed by pelvic EBRT with VMAT on a conventional Linac (45 Gy in 25 fractions) and finally a sequential oMRgRT boost to the vaginal vault recurrence (28 Gy in four fractions). Vaginal vault BT was considered but not deemed feasible since a complex interstitial approach under

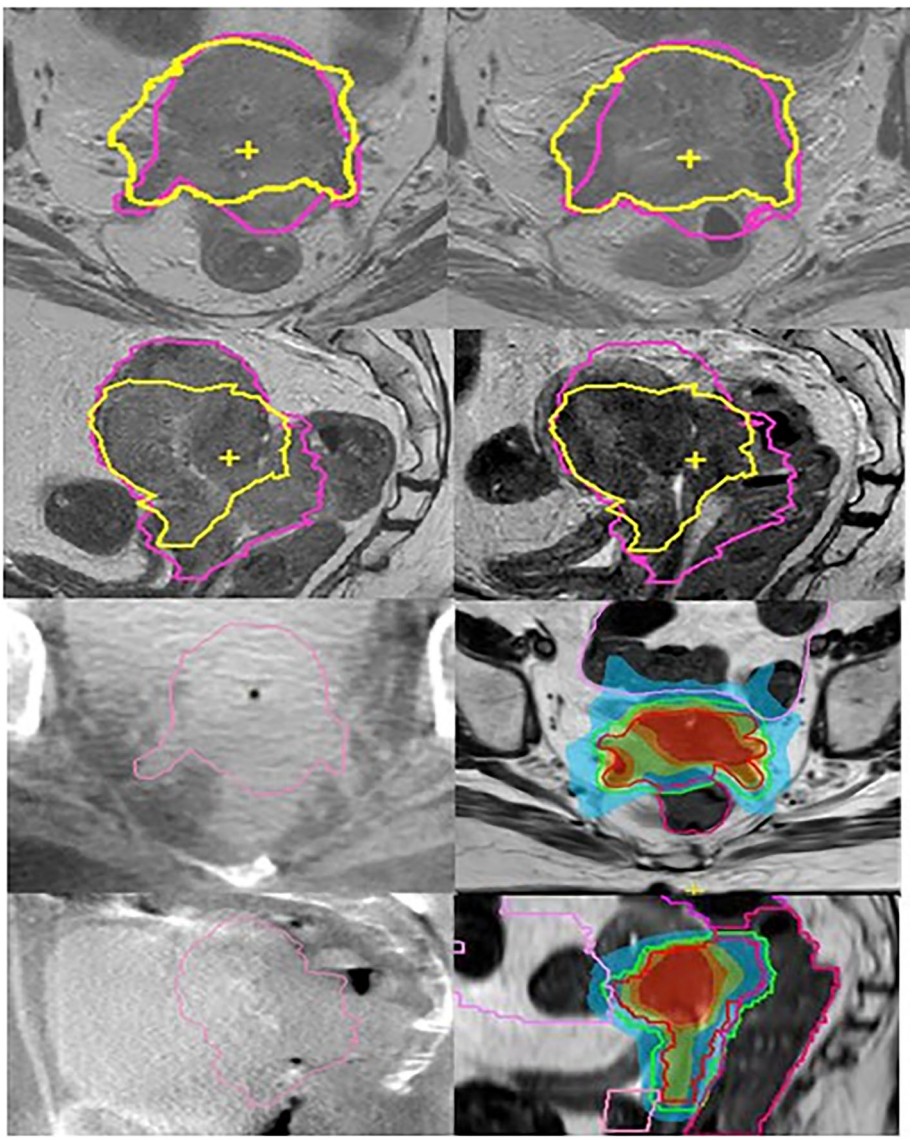

FIGURE 3 | Cervix cancer; MR linac boost of HR-CTV after pelvic EBRT. Left column (top to bottom) transversal and sagittal T2 weighted MRI at time of treatment planning and on-board CBCT scans in the first week of elective EBRT. Right column (top to bottom) MRI scans after 32.4 Gy of elective EBRT and first. MR Linac boost plans. For comparison reasons, the initial and boost HR-CTV contours are shown on the MRI scans (pink at time of treatment planning and yellow after 32.4 Gy EBRT). On the CBCT scans initial HR-CTV is shown. For the MR Linac boost plan, the online delineation of the first fraction for HR-CTV and rectum is shown. The images show the improved visualization of MRI compared to CBCT.

anesthesia would have been necessary and was not doable due to comorbidity.

A composite was done for each of the three radiotherapy courses (see **Figure 4**).

An isotoxic approach was used, giving the priority to OAR dose constraints during the planning process. The initial prescription (sum of EBRT and four boost fractions) to the vault recurrence (HR-CTV) was 91.9 Gy (D90%, EQD2 α/β 10), whereas the total dose delivered to this volume based on the sum of daily online planning was 82 Gy (D90%, EQD2 α/β 10). For D2 cc bladder and rectum, the pretreatment and online doses were 84.9 Gy/73.5 Gy and 68.3 Gy/73.7 Gy (D2cc, EQD2, α/β 3), respectively. The differences in pretreatment and online dose were mainly caused by variations in rectum positions and filling status, which in our isotoxic planning approach resulted in a reduced target dose.

For the abdominal wall metastasis, the SBRT planning aim was 35 Gy in five fractions to 95% of the target. For both pretreatment and online plan, the GTV35Gy (EQD2 α/β 10 = 50Gy) had a median value of 100%.

MRI done 3 months after treatment showed no residual tumor in both locations and no evidence of disease progression. So far, patient did not report unexpected or grade ≥3 treatment toxicity.

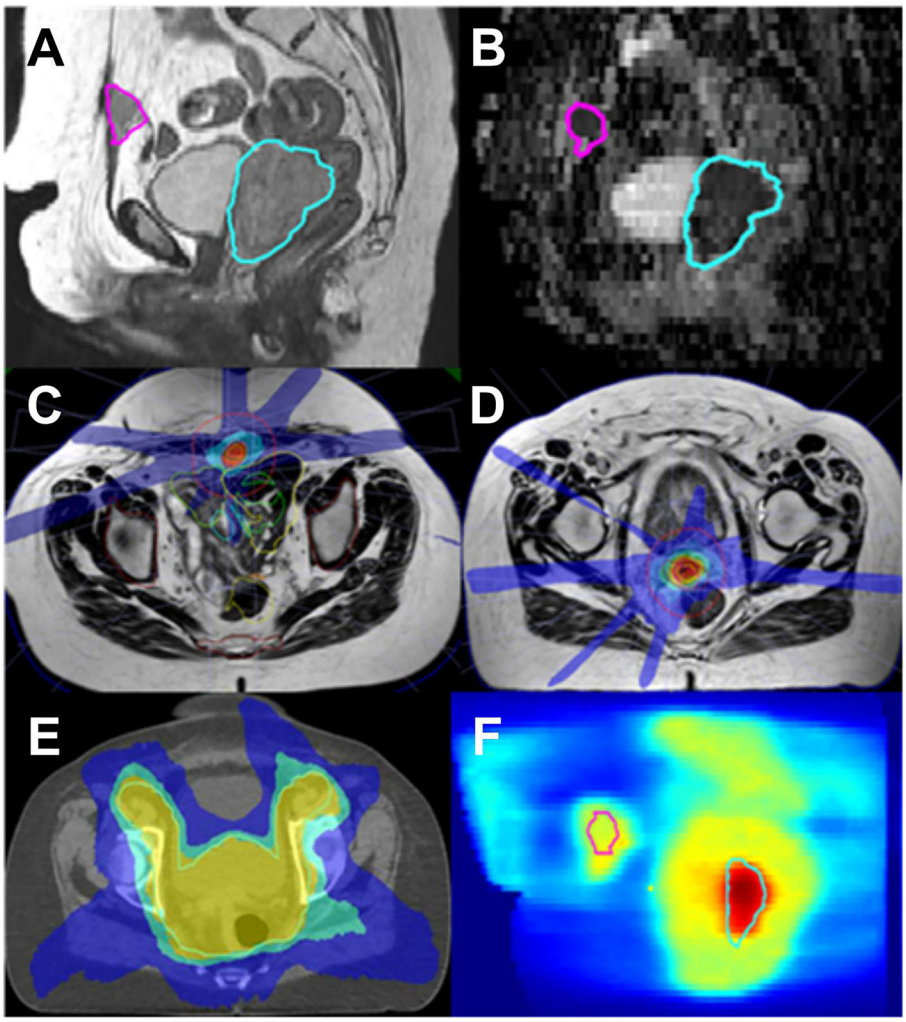

FIGURE 4 | Endometrial cancer; MR Linac SBRT for concurrent vaginal vault recurrence and anterior abdominal wall metastasis. **(A)**: T2 sagittal **(B)**: ADC map derived from diffusion weighted acquired with MR Linac. Abdominal metastasis in pink and vaginal vault recurrence in blue. Target and OAR are clearly visualized on the MR images allowing for daily adaptation. **(C, D)**: Typical daily MR Linac plans for both lesions (isodoses red 110%, orange 100%, blue 25%). **(E)**: elective EBRT plan on planning CT (yellow 95%, green 82%, blue 52%) **(F)**: overlay of elective and boost plans (range 0–70 Gy physical dose).

Case Example 3: Ovarian Cancer; Paraaortic Oligometastatic Relapse

A 51-year-old patient presenting with PAO relapse from ovarian cancer after previous treatment including primary surgery, chemotherapy, and targeted treatments at the time of 2nd and 3rd relapse. Surgery or further systemic treatment was not considered feasible at this time. Three PAO nodes in very close proximity to the duodenum were treated with oMRgRT. Five fractions were delivered using daily online ART to create nine-field IMRT plans with a stereotactic dose distribution. GTV-PTV

TABLE 1 | Case example 3: DVH parameters for planned *versus* accumulated dose from online adaptive treatment plans (total dose delivered with five fractions SBRT).

	Dose Prescribed (Gy)	Dose Delivered (Gy)	EQD2* Per prescription (Gy)	EQD2* Delivered (Gy)
GTV1 D100%	34.0	33.2	47.5	46.2
GTV2 D100%	34.7	34.3	49.0	48.2
GTV3 D100%	37.6	34.8	54.8	49.2
Duodenum D0.5cc	34.8	34.9	69.2	69.7
Duodenum D5cc	28.8	29.7	50.5	53.2

**For EQD2 calculations a/ß = 10 for GTVs and a/ß = 3 for OAR was applied.*

margin was 3 mm. Dose prescription was: GTV V35Gy = 100%, PTV V35 Gy > 95%, PTV D0.1cc < 47.25 Gy. Constraints for the duodenum were D0.5cc <35Gy and D5cc <25Gy (**Figure 5**).

Total target and OAR dose as calculated for the pretreatment plan and the five online adaptive plans for target lesions and the duodenum are shown in **Table 1**. The dose distribution had to be balanced between adequate target dose coverage and OAR constraints, resulting in a slightly lower dose for the three GTVs and a slightly increased dose for the duodenum. **Figure 5** shows target delineation and dose distributions of the five fractions.

At 2 months post treatment, patient is in good condition without any early treatment toxicity.

DISCUSSION

The introduction of oMRgRT in radiation therapy clinics brings opportunities to improve the accuracy of EBRT for the treatment of mobile soft tissue primary tumors and distant metastases. Combining high-quality on-board imaging and adaptive therapy capabilities is of high value for soft tissue tumor prone to have significant inter-fraction or intra-fraction motion.

Gynecologic tumors fit in this category of cancers as the surrounding OAR can cause considerable target deformation and position changes. Surrounding pelvic organs can move closer to the target compared to the original reference plan, and finally tumor volumes and shapes often change significantly during treatment.

During the last two decades, repeating MRI studies through the course of treatment and implementing an adaptive treatment planning strategy have led to improved BT treatment outcomes (5). IGABT has been shown to be associated with improved tumor control and better survival (7, 9, 10, 31). The early experience with the use of MR Linac systems, described in this manuscript, demonstrates that oMRgRT has the potential of improving EBRT outcomes as well (15, 26, 61, 65).

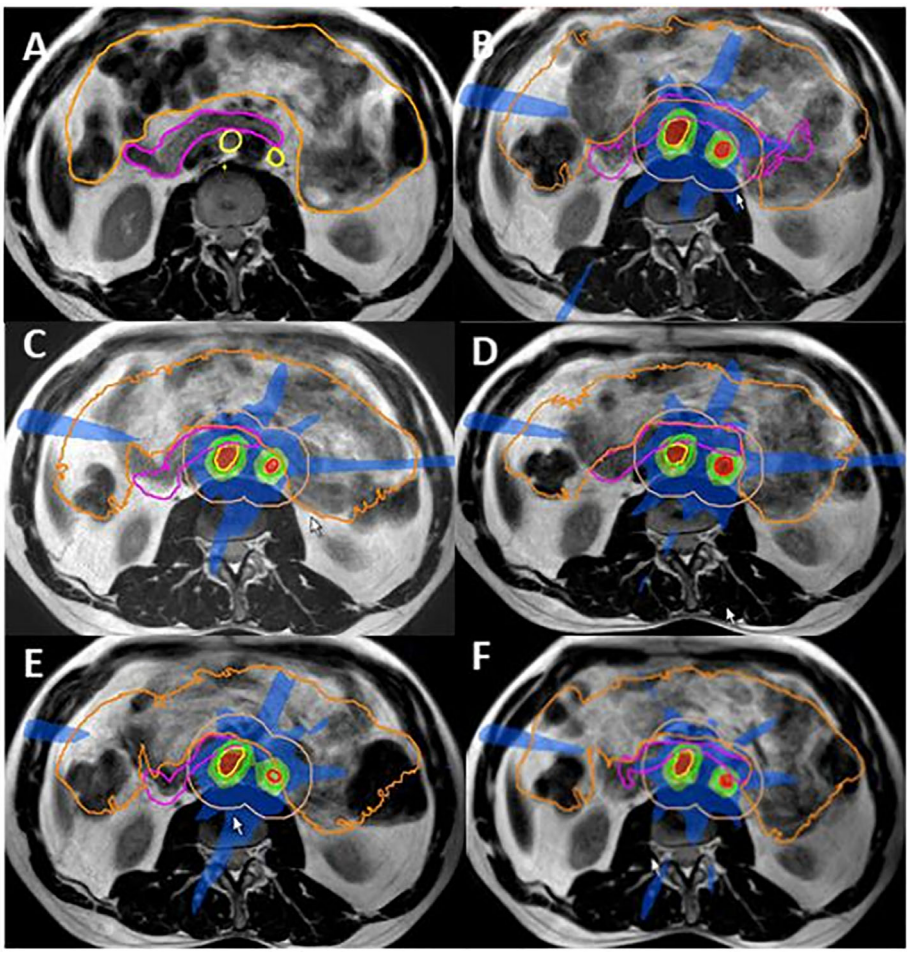

FIGURE 5 | Ovarian cancer MR Linac SBRT for PAO oligometastatic relapse. **(A)** Contours delineated for pretreatment planning GTV1 and GTV2 yellow; duodenum pink, bowel orange. **(B–E)**: Online dose distribution for fractions 1–5, GTV1 and GTV2 (red) and PTV1 and PTV2 (green) with 2 cm ring for online contouring and planning guidance orange. Within the ring structure, target structures were manually adapted for the duodenum (pink) and bowel bag (orange) after an initial automated deformation of the contours; **(F)** individual dose distribution with dose levels shown as percentage of 35 Gy (5 × 7 Gy) prescribed dose red 110%, orange 100%, light green 75%, and blue 50%.

LACC is a key example of tumors which could benefit from the use of oMRgRT, given the better soft tissue visualization provided by on-board MRI compared to CBCT, and the possibility to correct for any target motion and changes in surrounding organs position on a daily basis. Single-institution experience as described in this manuscript indicates that it is possible to use MR Linacs for pelvic radiation during a course of curative treatment for cervical cancer. The restricted length of treatment fields of the current MR Linac systems, however, brings limitations when extended field RT is required. In the future, solutions like VMAT combined with a tomotherapy approach would be of utmost interest to allow for treatment of larger volume. The treatment field size limitation of MR Linacs currently prohibits the use of MRg when either the high common iliac or the PAO nodes need to be treated, which is frequent in the management of LACC. This is a clinical situation where better conformity of radiation dose distribution is especially needed, since the radiation tolerance of the surrounding organs (small bowel loops, particularly the duodenum, kidneys) is low (88), while high dose of radiation is needed for tumor control. Better dose conformity is especially needed when chemotherapy is combined with extended field RT or in cases of oligometastic PAO disease. In both situations, patients will benefit from more conformal dose distributions that allow for dose escalation with a broader therapeutic window. When multiple targets need to be treated (synchronous treatment of primary tumor and multiple affected nodes or oligo metastases), MR Linac treatments, with the possibility to perform adaptive plan daily and use smaller treatment margins, are of interest (65).

While MR Linac systems (Unity/Elekta Sweden or MRIdian/ViewRay Cleveland, OH, USA) were the first radiation delivery systems with online adaptive capabilities, there is now a CBCT-based Linac (ETHOS, Varian, Paolo Alto, CA, USA). The strength and limitations of each technology will become clearer as we gain more clinical experience using these systems. Inferior soft tissue contrast might be a limiting factor to perform ART with the CBCT Linac option.

Online ART requires recontouring and replanning while the patient is on the table; therefore, extended treatment time is a concern for the clinical implementation. More experience will be needed to prove if ART could lead to improved treatment outcomes and if the benefit of this treatment approach outweighs the cost on department resources. Successful attempts to automate delineation and increase speed of planning software would affect this balance.

When treating gynecological cancers, radiation boosts are frequently used to treat the primary tumors or central local recurrences. BT (preferably IGABT) is the treatment modality of choice to deliver these boosts and should be applied whenever feasible. However, there are some frail patients for whom invasive procedures cannot be done, and there are clinical situations where the extension of the disease is unfavorable for an adequate implant. In these situations, oMRgRT can be used to deliver highly conformal external beam boosts. As a starting point, traditional dose constraints that are used for hypofractionated BT SBRT should guide the selection of oMRgRT boost dose and fractionation prescription (26).

Based on treatment planning comparisons and initial clinical experience, the therapeutic window of oMRgRT boosts is not as good as optimal BT but compares favorably to non-adaptive CBCT-guided plan.

In conclusion, oMRgRT provides options for the delivery of more conformal therapy using an ART approach for patients with gynecological cancers in different disease stages. Future clinical experience will confirm if the expected gain in treatment conformity will translate into improved clinical outcomes. For the management of central pelvic disease, BT is the most conformal treatment technique to deliver an ablative dose to the tumor, and oMRgRT boosts should not replace BT in situations where it is feasible, due to the well-documented success rates achieved with BT (10).

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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