Review Article

MR-linac based radiation therapy in gastrointestinal cancers: a narrative review

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background and Objective: Magnetic resonance guided radiotherapy (MRgRT) is an emerging technological innovation with more and more institutions gaining clinical experience in this new field of radiation oncology. The ability to better visualize both tumors and healthy tissues due to excellent soft tissue contrast combined with new possibilities regarding motion management and the capability of online adaptive radiotherapy might increase tumor control rates while potentially reducing the risk of radiation-induced toxicities. As conventional computed tomography (CT)-based image guidance methods are insufficient for adaptive workflows in abdominal tumors, MRgRT appears to be an optimal method for this tumor site. The aim of this narrative review is to outline the opportunities and challenges in magnetic resonance guided radiation therapy in gastrointestinal cancers.

Methods: We searched for studies, reviews and conceptual articles, including the general technique of MRgRT and the specific utilization in gastrointestinal cancers, focusing on pancreatic cancer, liver metastases and primary liver cancer, rectal cancer and esophageal cancer.

Key Content and Findings: This review is highlighting the innovative approach of MRgRT in gastrointestinal cancer and gives an overview of the currently available literature with regard to clinical experiences and theoretical background.

Conclusions: MRgRT is a promising new tool in radiation oncology, which can play off several of its beneficial features in the specific field of gastrointestinal cancers. However, clinical data is still scarce. Nevertheless, the available literature points out large potential for improvements regarding dose coverage and escalation as well as the reduction of dose exposure to critical organs at risk (OAR). Further prospective studies are needed to demonstrate the role of this innovative technology in gastrointestinal cancer management, in particular trials that randomly compare MRgRT with conventional CT-based image-guided radiotherapy (IGRT) would be of high value.

Keywords: Magnetic resonance guided radiotherapy (MRgRT); stereotactic body radiotherapy (SBRT); image-guided radiotherapy (IGRT); gastrointestinal malignancies; online adaptive radiation therapy

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Submitted Sep 29, 2022. Accepted for publication Aug 14, 2023. Published online Sep 01, 2023.
doi: 10.21037/jgo-22-961
View this article at: https://dx.doi.org/10.21037/jgo-22-961

Introduction

Magnetic resonance-guided radiotherapy

Conventional linear accelerators (linacs) use different techniques to deliver image-guided radiotherapy (IGRT), ensuring precise dose delivery. Current standard is on-board cone-beam computed tomography (CBCT), which allows effective matching of bone structures but has severe limitations distinguishing tumor from surrounding organs at risk (OAR) due to poor soft-tissue contrast. Furthermore, noise and artifacts can negatively influence image quality of CBCT. The major goal of modern radiation therapy techniques is to deliver high doses precisely to tumor tissue, while sparing the OAR. To compensate for uncertainties of CT-based IGRT methods, larger planning target volume (PTV) margins can be chosen. Sometimes, the close proximity of target volumes and healthy tissues, however, makes it impossible to safely apply high doses to the tumor with sufficient target coverage. This aspect is even more important when applying stereotactic body radiotherapy (SBRT), which demands precise image-guidance, as sharp dose gradients with central dose increase are used to deliver ablative doses in only a few fractions. MR-linacs are hybrid systems that combine a linear accelerator with an on-board magnetic resonance imaging (MRI) scanner. Compared to CT imaging, MRI provides superior soft tissue discrimination, which is particularly helpful in cancer sites surrounded by soft tissue organs, such as the abdominal or pelvic region. Before the clinical introduction of MR-linacs, the role of MR imaging in RT planning remained limited to initial target volume delineation before treatment start or diagnostic MR imaging being incorporated into offline adaptation workflows. MR-guided radiotherapy (MRgRT) implies that MR imaging can be acquired not only before and after an RT treatment, but also during the treatment, providing real-time imaging which paves the way to new motion management approaches both in terms of tracking anatomical motion of OARs and the possibility of respiratory or non-respiratory gating. MR imaging being non-ionizing enables a safe acquisition of real-time imaging for motion management. Real-time MR imaging and gating enables a reduction of PTV margins, reducing OAR doses while ensuring accurate dose delivery to the target volume. Considering these innovative options, invasive fiducial implantations become unnecessary in MRgRT. Furthermore, the MR-linac workflow allows for online plan adaptation with the patient remaining on the linac's treatment table. Online adaptive radiation therapy (ART) enables radiation oncologists to dynamically adjust to the patient's anatomy of the day by recontouring OAR and target volumes followed by recalculation of dose distributions on the anatomy of the day. Real time imaging and gating can also be assisted by video feedback systems, which enables patients to take an active role in their treatment procedure. This aspect was reported to yield high patient satisfaction in prospective observational study with regard to MR-linac patient tolerance (1).

At the time of writing this review, three MRgRT devices are commercially available. The MRIdian system is manufactured by ViewRay (Viewray Technologies Inc, Oakwood Village, Ohio, USA) and uses a 0.35 T MRI scanner with three ^{60}Co γ-ray sources or a 6 MV Flattening Filter Free (FFF) linac for radiation delivery (2,3). The Unity MR by Elekta (Elekta AB, Stockholm, Sweden) combines a 1.5 T MRI scanner with a 7 MV FFF linac (4,5). The third system, Aurora-RT, received FDA approval in 2022 (MagnetTx Oncology solutions, Edmonton, Alberta, Canada) (6). At least one other device is in development: the Australian MRI-linac Program (Ingham Institute, Liverpool, NSW, Australia) (7). The available systems by Elekta and Viewray currently apply intensity modulated radiotherapy (IMRT) using the step-and-shoot technique without the ability of performing more complex modulation approaches such as sliding window IMRT or volumetric modulated arc radiotherapy (VMAT). The Aurora-RT system is capable of VMAT, according to the manufacturer.

This review focusses on gastrointestinal cancer sites, which represent one of the most interesting applications of MRgRT as this anatomical region is demanding to radiation oncologists considering the potential proximity of tumor tissues and OAR and the need of motion management. Not only is there anatomical variability of hollow organs such as stomach, duodenum or bowel loops, but also can OAR and target volumes be strongly affected by breathing cycle phases. Therefore, MRgRT appears to be highly suitable to address these challenges. We present this

Table 1 The search strategy summary

Items	Specification
Date of search	13 August 2022
Databases and other sources searched	PubMed
Search terms used	"MR-guided radiotherapy", "MR-linac", "pancreatic cancer", "rectal cancer", "liver metastases", "hepatocellular carcinoma", "esophageal cancer"
Timeframe	01 Jan 2015 to 13 Aug 2022
Inclusion criteria	Studies conducted in patients with gastrointestinal malignancies or metastases, treated with MRgRT. Reviews focusing on MRgRT and/or the technological background of MRgRT
Selection process	Eligible articles were screened by all authors

MRgRT, magnetic resonance guided radiotherapy.

article in accordance with the Narrative Review reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-961/rc).

Methods

Table 1 shows the search strategy summary. Eligible articles were screened by all authors. The focused keywords were "MR-guided radiotherapy", "MR-linac", "pancreatic cancer", "rectal cancer", "liver metastases", "hepatocellular carcinoma" and "esophageal cancer". We included studies conducted in patients with the mentioned tumor entities receiving MRgRT, reviews investigating MRgRT in general or specific gastrointestinal tumor sites and articles related to the technological background of MRgRT as well as dosimetric considerations. The articles were limited to full-text publications in English.

Discussion

Pancreatic cancer

Pancreatic cancer is one of the most aggressive tumor entities with a 5-year survival rate of approximately 10% in the USA (8). Surgery is the treatment of choice for localized disease, but more than 80% of diagnosed patients present with locally advanced or metastasized disease (9). The role of chemoradiation in surgically unresectable patients is controversial. The LAP07 study showed no significant difference in overall survival (OS) with the combination of chemotherapy and radiotherapy (CRT) compared to chemotherapy alone but improved local control for patients treated with CRT (10). The Eastern Cooperative Oncology Group (ECOG) trial even demonstrated improved OS with the addition of radiotherapy to Gemcitabine compared to Gemcitabine alone (11). Moreover, the GERCOR studies suggested an overall survival improvement with CRT compared to chemotherapy alone (12). The impact of hypofractionated radiotherapy alone or in combination with chemotherapy in locally advanced pancreatic cancer (LAPC) has been investigated in several studies. OS may be improved, but considering the highly radiosensitive surrounding healthy tissues, dose escalation is difficult to achieve, and the risk of toxicity remains high (13-18).

An important aspect of safe and efficient treatment delivery in radiotherapy of pancreatic cancer is motion management. Breathing and bowel movements can result in dislocation of the target volume and OAR during beam delivery and interfractionally. Respiratory-induced dislocation of the pancreas alone was quantified by Karava *et al.* using 4D-CT imaging reporting up to 4.8 mm movement in inferior-superior direction (19). MRgRT therefore seems to be an ideal approach for hypofractionated RT in pancreatic cancer as the online adaptive workflow combined with the gating capabilities and advantages in MR-based segmenting addresses the known deficiencies of conventional CT-based radiotherapy in this tumor site. Nevertheless, only few clinical trials have systematically investigated MRgRT in this patient group, yet.

MRgRT in pancreatic cancer

In a prospective phase I trial, Henke *et al.* have treated 20 patients with oligometastatic or unresectable primary abdominal malignancies with stereotactic MR-guided adaptive radiation therapy (SMART), 5 of which had primary or recurrent pancreatic adenocarcinoma (20). The

primary endpoint of their study was the achievement of adaptive treatment delivery in less than 80 min on-table time per fraction for >75% of all cases. All 20 radiation therapy plans were prescribed with a dose of 50 Gy in 5 fractions. Of all adapted fractions, 75% were adapted to meet OAR constraints, mostly due to small bowel constraint violations. In 43% of all fractions, PTV dose de-escalation was necessary to meet OAR constraints whereas dose-escalation beyond 10 Gy/fractions was possible only for three patients but none of the pancreatic cancer cases. Improvement of PTV coverage by online adaptation was achieved in 57% of cases. No grade 3 toxicity (CTCAE v4) was reported. Two of the patients with recurrent LAPC experienced progression at 15 months of follow-up, whereas both patients with primary LAPC were alive without progression at 50- and 56-weeks follow-up. This study suggests that adaptive MRgRT may be a feasible approach for inoperable pancreatic cancer patients.

Rudra *et al.* have retrospectively analyzed 44 patients with unresectable pancreatic cancer treated with MRgRT in an international multi-institutional cohort study (21). Patients were treated with either conventional fractionation (40–55 Gy in 25–28 fractions), hypofractionation (50–67.5 Gy in 10–15 fractions) or two differing SBRT schemes (30–35 Gy in 5 fractions or 40–52 Gy in 5 fractions). Adaptive treatment was used for patients who received 15 or fewer fractions. Patients were stratified into high-dose [biologically effective dose (BED_{10}) >70 Gy] and standard-dose groups (BED_{10} ≤70 Gy). The 2-year OS was significantly improved (49% *vs.* 30%, P=0.03) in patients treated with a BED_{10} >70 Gy compared to the standard-dose group after a median follow-up of 17 months. No grade 3 or higher gastrointestinal toxicity was reported in the high-dose group but in three patients in the standard-dose group. Online-adaptation was more frequent in the high-dose group (83%) compared to the standard-dose group (15%). Rudra *et al.* demonstrated that MRgRT is a safe approach for ablative dose escalation in LAPC patients and that higher BED_{10} is associated with improved OS and freedom from local failure (FFLF). A prospective phase II multicenter study investigating MRgRT with 50 Gy in 5 fractions for inoperable pancreatic cancer patients has been initiated by the authors (NCT03621644).

A retrospective analysis of 35 pancreatic cancer patients treated with stereotactic MRgRT using adaptive planning was published by Chuong *et al.* in 2021 (22). Most of the patients (91.4%) had induction chemotherapy before radiotherapy. A median dose of 50 Gy was inhomogeneously prescribed in 5 fractions, allowing hotspots of 120% to 130%. Interestingly, 57.1% of these patients had elective nodal irradiation. Grade 3 toxicity rates were low with 2.9% both acute and late events. After a median follow-up of 10.3 months, 1-year OS was 58.9%, local control was 87.8% with a median time to local progression of 7.4 months. Distant metastasis-free survival and progression-free survival were 63.1% and 52.4%, respectively. The same group published retrospective data of a large LAPC patient collective of 62 patients who received induction chemotherapy followed by stereotactic adaptive MRgRT with a median dose of 50 Gy (range, 40–50 Gy). The 2-year local control, progression-free survival and OS were 68.8%, 40.0% and 45.5%, respectively. Rates for acute and late grade 3+ toxicity were 4.8% and 4.8%, respectively (23).

A first series of 10 patients with abdominal tumors treated with MRgRT with a 1.5 Tesla MR-linac without the ability of gating and automated beam delivery was published by Hall *et al.* (24). Two out of three pancreatic cancer patients had local recurrences, one had primary pancreatic adenocarcinoma and a solitary liver metastasis. Prescribed doses were 30–33 Gy in 5–6 fractions. Treatments were reported to be feasible without any significant acute toxicities.

Hassanzadeh *et al.* published another series of 44 patients with inoperable pancreatic adenocarcinoma treated with stereotactic MRgRT with 50 Gy in 5 fractions in 2021 (25). They report 4.6% late grade 3, a median OS of 15.7 months and a 1-year local control of 84.3%. Median follow-up here was 16 months.

While online adaptive MRgRT offers new opportunities from a radiation oncologist's perspective, it is also complex and time-consuming as the workflow requires various steps including re-contouring of OAR and target volumes, evaluation of the initial plan and re-optimizing the dose distribution if necessary, online quality assurance (QA) and finally beam delivery (26). Furthermore, real-time tracking and beam gating inevitably decrease beam on duty cycle. Lamb *et al.* reported a median time for the full fraction of 54 min in 80 cases, contouring being the most time-consuming step with a mean time of 22 min (27). In Henke's phase I trial, the mean duration per fraction was even 80 min, but still well tolerated by the patients (20).

Addressing the aspect of OAR recontouring, Bohoudi *et al.* have introduced an ART online strategy which requires only limited re-delineation (28). Their proposal for SMART is to only adjust OAR within a distance of 3 cm from the PTV ($SMART_{3cm}$). In order to test this strategy, the Dutch group compared plans of 50 fractions treating

LAPC, that had been delivered at their institution using the $SMART_{3CM}$ approach, against a simulated standard (re-)planning method using full-scale OAR re-delineation (FULLOAR) with optimization objectives applied to the entire OAR. Dosimetric assessment included comparison of PTV coverage (V95%, D_{mean}, D_{1cc}) and OAR constraints. The $SMART_{3cm}$ strategy resulted in lower high- and intermediate-dose exposure to all OARs compared to the FULLOAR approach, which also didn't meet the V_{33Gy} dose constraint in 36% of the fractions. Considering the reduced time required, the Dutch $SMART_{3CM}$ strategy has been adopted by many institutions using online adaptive MRgRT. The same group later published a dosimetric analysis of 180 fractions treating 36 LAPC patients with MRgRT prescribed with 40 Gy in 5 fractions (29). Gross tumor volume (GTV) coverage and OAR high-doses were compared in non-adapted and re-optimized plans, as well as the compliance with their institutional objectives for GTV coverage and high-dose OAR constraints. Using the adaptive workflow resulted in an increase from 43.9% to 83.3% of plans meeting the institutional constraints after adaptation. GTV coverage and OAR V33Gy doses could significantly be improved. Using their approach of characterizing adaptation as "beneficial", "not needed" or "no benefit", adaptive planning was beneficial in 52.8%. A close proximity of ≤3 mm distance between GTV and adjacent OAR was the major relevant factor in achieving an advantage through adaptation.

Following a similar ART workflow, Placidi *et al.* were able to show dosimetric advantages of online adaptive treatment in pancreatic cancer SBRT (30). In a series of 8 patients with a total of 38 fractions (30–40 Gy in 5 fractions) 68.4% of all fractions were adapted online. ART led to a mean PTV V95% increase of 10.8% and clinical tumor volume (CTV) V98% increase of 12.6%. There was also a trend towards reduced V33 and V25 for all OARs. These results were confirmed by Michalet *et al.* in a recently published prospective registry study with 30 patients with pancreatic tumors, who were treated with stereotactic MRgRT in 5 fractions with a median dose prescription of 50 Gy (31). All 150 fractions in this series were adapted because of improvements on PTV coverage or on OAR dose exposure. Adapted plans had a statistically significant mean V95% increase of 2.2% compared to predicted plans, with optimized PTV (optimization structures were generated by subtracting digestive OAR + 5 mm from the PTV) V95% coverage even increased by 4.3%. Also, a significant decrease of dosimetric measures could be seen for OAR in adapted plans. None of the patients experienced grade >2 acute toxicities and after a median follow-up of 9.7 months, the median OS for the whole cohort was 14.1 months. The 6-month and 1-year OS from radiotherapy were 89% and 75%, respectively. 42.1% (8 out of 19) of the patients with initial LAPC and 33.3% (1 out of 3) of patients with initial borderline resectable pancreatic cancer (BRPC) had surgery after stereotactic MRgRT, all with negative margins (R0).

In a retrospective evaluation, Tyran *et al.* analyzed whether a radiation oncologist's decision to create a predicted plan on the MRI of the day or not, resulting in delivery of the non-adapted baseline plan, was consistent when comparing this strategy to an offline adaptive workflow (32). Their online adaptive workflow was based on the visual review of MRI imaging of each fraction. The offline strategy consisted of re-calculation of a predicted plan with full offline re-contouring followed by evaluation of the predicted dose-volume histograms (DVH). In their series of 35 fractions of stereotactic MRgRT of pancreatic cancer, a total decision mismatch of 37% was reported. The authors conclude that sole visual review of daily MR images is not sufficient to determine if plan adaptation would be beneficial and therefore recommend generation of online predicted plans daily for every fraction.

To our knowledge, there have been no randomized trials comparing MR image guidance and CT image guidance for LAPC treatment, so far, which would be helpful to further quantify the benefit of MRgRT in this tumor site. Kim *et al.* have published a case report of a successful treatment of a patient with pancreatic cancer treated with cone beam computed tomography-guided stereotactic adaptive radiotherapy (33). Although the patient samples in literature are small, promising results regarding toxicity, tumor control and survival rates were reported for adaptive MRgRT in pancreatic cancer. A prospective, randomized controlled trial comparing induction chemotherapy followed by stereotactic MRgRT with 50 Gy in 5 fractions and induction chemotherapy alone is estimated to start recruiting in July 2023 (NCT05585554). Large prospective trials and close collaboration with medical oncologists and surgeons will be needed to establish the future role of this auspicious technology in the clinical management of pancreatic cancer.

Liver metastases and primary intrahepatic tumors

Liver metastases and hepatocellular carcinoma undoubtedly represent a very important application of MRgRT, as

MR imaging is a key asset in the diagnosis and further characterization of intrahepatic lesions and the role of SBRT in their treatment (34-36). For oligometastatic disease, SBRT has proven to be an important treatment option (37). For primary liver cancer and liver metastases, a surgical approach is still the preferred treatment in many situations, assuming a medically operable patient. For liver metastases from colorectal cancer (CRC), 10-year survival rates of 17% can be achieved in selected patients (38). In patients with hepatocellular carcinoma, 5-year survival rates of 50% and even 74% 4-year survival after liver transplantation have been reported (39-41). For small liver tumors in patients who are not suitable for surgery due to comorbidities or limited liver function, there are many local treatment options, such as radiofrequency ablation (RFA), microwave ablation (MWA), percutaneous ethanol injection (PEI), interstitial brachytherapy (IBT), transarterial chemoembolization (TACE) or Yttrium-90 transarterial radioembolization (40,42). SBRT can be an effective local treatment option with its ability to deliver ablative doses in a highly conformal and precise way, therefore sparing healthy liver tissue and reducing the risk of radiation-induced liver disease (RILD) (43).

SBRT of primary liver tumors

The role of SBRT in primary liver cancers is still inconclusive (44). Surgery is usually the treatment of choice. If resection or percutaneous ablative therapies are not suitable (e.g., due to location or size of the tumor) or rejected by the patient, SBRT is the preferred therapeutic option, particularly in early-stage disease and when tumor size is small. Ablative radiation therapy is also used as a salvage treatment of recurrences after failure of other local therapies or in case of residual tumor lesions after primary therapy (45). Patients with limited liver reserve, who are listed for liver transplantation, may benefit from SBRT as a bridging therapy, as these patients would experience higher toxicities after primary SBRT (46,47). Studies that have compared SBRT with RFA and SBRT in combination with TACE versus TACE alone have demonstrated the safety and excellent efficacy of SBRT, even when prior local therapies had been applied (48-50). SBRT has also been reported to be an effective option in patients with portal vein tumor thrombosis (PVTT), which precludes surgery or TACE (51,52). There is only few data available investigating the role of SBRT in patients with cholangiocarcinoma, but promising local control rates have been reported for selected patients, in particular when combined with adjuvant chemotherapy (53).

SBRT of liver metastases

Studies analyzing the effectiveness of SBRT in unresectable liver metastases have demonstrated promising local control rates with low treatment-related toxicities (54,55). Local control seems to be depending on the prescribed dose and tumor volume (36,56). As dose escalation can be difficult due to proximity of radiosensitive OAR or limited liver reserve with increased risk of RILD, the treatment of choice should always be based on a multidisciplinary assessment of the individual patient. In larger lesions, SBRT has been shown to be superior to MWA in terms of 1-year freedom from local progression (FFLP) (57,58). Both RFA and SBRT can be options in patients with multiple liver metastases when a radical local approach is chosen (59).

MRgRT in primary and secondary liver tumors

Many primary and secondary liver tumors can only poorly be visualized by standard CT imaging. Clearly, the liver is an anatomical site which is highly movable itself and OAR such as bowel loops, duodenum or the stomach can be particularly close to this organ, restricting the delivery of ablative doses to liver tumors. Due to its excellent soft-tissue contrast, MRgRT is suitable for liver lesions, even if a lesion is not visible on the simulation MR scan, as indirect target gating can also be an option (60). Another option to better visualize liver metastases can be utilization of intravenous contrast (61).

In 2015, Kishan *et al.* reported on a small cohort of 16 patients with malignant hepatic lesions treated with Tri-Cobalt-60 MRgRT with 36 to 60 Gy in 3–5 fractions (62). Liver and kidney sparing was comparable to conventional linac plans when the lesions were smaller or more peripherally located.

A multi-institutional study by Rosenberg *et al.* assessed the outcomes of 26 patients treated with stereotactic MRgRT [6 hepatocellular carcinomas (HCC), 2 cholangiocarcinomas and 18 liver metastases] (63). The median delivered dose was 50 Gy in 5 fractions and median liver dose 12.7 Gy (3.2–21.9 Gy). At a median follow-up of 21.2 months, the FFLP was 80.4% and the 1- and 2-years OS were 69 and 60%, respectively. Two patients experienced grade 3 gastrointestinal toxicity, both having undergone prior local liver therapies.

Twenty-nine patients with HCC [26], cholangiocarcinoma [2] and liver metastases [1] were investigated in a trial by Feldman *et al.*, treating 34 lesions in total (64). The dose

prescribed ranged between 45 and 50 Gy in 5 fractions (31 lesions) and between 27 and 42 Gy in 3 fractions (3 lesions). The mean liver dose was 5.56 Gy (1.39–10.43 Gy). No grade 3 toxicity was reported in this cohort. All except one patient had stable or decreased size of the treated lesions in follow-up imaging at 1 to 12 months after therapy. The SMART approach for abdominal malignancies published by Henke *et al.* included five patients with HCC, one patient with cholangiocarcinoma and four patients with liver metastases (20). None of the patients in this cohort experienced any grade 3 toxicity. The 6-month local progression free survival rate and 1-year OS were 89.1% and 75%, respectively. Hall *et al.* reported on their experience treating 10 patients with abdominal tumors with a 1.5 T MR-linac (24). Two of those patients had HCC, four had liver metastases. Doses for HCC patients ranged between 40 and 45 Gy in 5 fractions, doses for liver metastases between 45 and 60 Gy in 3 fractions. 4D-CT and 4D-MR imaging was part of the RT simulation, resulting in an internal target volume (ITV) approach. An adaptive workflow based on adapt-to-position (ATP, online plan adaptation is performed based on the new patient position and optimized on the pre-treatment CT and contours) or adapt-to-shape plan adaptation (ATS, online plan adaptation is performed on the new patient anatomy and optimized on the daily MRI and adapted contours) was used. At 7.2 months of follow-up, no grade 3 toxicity and no local progression were reported. In a retrospective analysis by Boldrini *et al.*, 10 patients with a total of 12 HCC lesions were treated with stereotactic MRgRT with a BED of >100 Gy in 5 fractions (65). At a median follow-up of 6.5 months, two cases of ≤ G2 toxicity were reported (fatigue and ascites) with a local control rate of 90%.

A cohort of 12 patients with unresectable extrahepatic and five patients with intrahepatic cholangiocarcinomas was investigated by Luterstein *et al.*, demonstrating promising results of MRgRT in this tumor entity (66). A median dose of 40 Gy in 5 fractions was prescribed. Median OS was 18.5 months, with a 1-year OS of 76% and 2-year OS of 46.1%. Local control rates after 1 and 2 years were 85.6% and 73.3%, respectively. One patient was affected by an acute grade 3 duodenal ulcer with perforation (6%), one more patient had a late grade 2 gastritis/colitis. In this cohort, adaptive planning was used after treatment of the first few patients. An entirely adaptive workflow for stereotactic MRgRT in primary and secondary liver tumors was used by Rogowski *et al.*, who published early results of SBRT in 11 patients (67). After a median follow-up of five months, no local failure and no ≥ grade 2 toxicity was seen here. A total of 15 lesions were treated with a median BED_{10} of 84.4 Gy (59.5–112.5 Gy) in 3–5 fractions. Notably, the median overall treatment time for the online adaptive workflow was 53 minutes. Another cohort of patients with HCC and liver metastases was reported on by Weykamp *et al.*, focusing not only on oncologic outcomes but also patient-reported outcomes (68). Twenty patients with 26 lesions were treated with online adaptive MRgRT with a median BED_{10} of 105.0 Gy (67.2–112.5 Gy). The median follow-up was 9.4 months, with a local control of 88.1% at 12 months and OS of 84.0%. Grade 2 gastrointestinal toxicity was observed in 5.0% of the patients, with no grade 3 or higher toxicity. Excellent local control rates of 94.7% after 1 year were reported by van Dams *et al.* for ultrahypofractionated MR-guided SBRT of 20 patients with 25 primary or secondary liver tumors (69). They prescribed a median dose of 54 Gy (11.5–60 Gy) in a median of 3 fractions (1-5). The median follow-up here was 18.9 months. Local control after 2 years was estimated 79.6%, without any acute grade ≥3 toxicities. One patient had late grade 3 duodenal ulceration with late grade 4 toxicity (sepsis). A plan review of this patient revealed that the V35Gy to a close loop of small bowel was 0,46 cm^3. A volumetric maximum dose constraint of 0.35 cm^3 was then implemented for 3-fraction SBRT.

There is only few data about the dosimetric advantages of online adaptive MRgRT for liver tumors. Mayinger *et al.* assessed 15 patients with oligometastatic liver metastases, comparing re-optimized plans based on the MRI of the day with rigidly shifted baseline plans (70). Parameters for GTV, PTV and OAR were analyzed. PTV coverage (V100%) was improved with re-optimized plans in 47 of 75 fractions and OAR dose exposure was reduced (D_{1cc}, D_{mean}) in 33 of 75 fractions compared to the non-optimized baseline plans. The extent of PTV coverage improvement was larger for metastases within close proximity of an OAR (4.0% improvement when ≤0.2 cm distance between OAR and PTV edge; P=0.01), whereas plans with metastases further away from OAR did not significantly benefit dosimetrically from plan adaptation. In a similar approach, Nierer *et al.* demonstrated that their subgroup of SBRT plans for liver tumors benefitted most with regard to GTV D98% (6.3% improvement) when comparing adapted plans with predicted baseline plans (71). To our knowledge, no data is available for a randomized comparison of CT-based and MR-guided SBRT for liver tumors. There is an ongoing study, however, randomizing patients with 1–3 liver

metastases between MRgRT and ITV-based SBRT at a conventional Linac in case BED_{10} ≥100 Gy is feasible with an ITV-based plan. If a BED_{10} of at least 100 Gy cannot be achieved, the patient will be treated with MRgRT at the highest possible dose (72). High level evidence is indeed needed to show clinical benefits of stereotactic adaptive MRgRT in liver tumors, although the existent data seems promising.

Rectal cancer

CRC is one of the most common tumor sites worldwide and represents the second most common cause of cancer death in the United States. Rectal cancer accounts for about one third of all CRC cases (8). In locally advanced rectal cancer (LARC), neoadjuvant chemoradiotherapy is the gold standard treatment, followed by total mesorectum excision (TME), which has led to significant improvement of local control (73,74). MR imaging is a key asset regarding the diagnostic accuracy of predicting the circumferential resection margin (CRM) status and is therefore a standard for local staging (75-77). A selective restriction of neoadjuvant chemoradiotherapy (nCRT) to high-risk patients based on pretherapeutic MR imaging has demonstrated good results and confirmed the need of high-quality MRI assessment in rectal cancer staging (78). It has recently been shown that quantitative analysis of MR imaging throughout MR-guided nCRT can be a valuable tool to predict clinical complete response (cCR) and pathological complete response (pCR) (79-81). In a similar radiomics approach, the early regression index (ERI_{TCP}) was used to predict pathological complete response, derived from early regression volume measured by 1.5 T staging MR imaging acquired before and during treatment, later also confirmed on 0.35 T MRgRT images (82,83).

In recent years, total neoadjuvant therapy (TNT) has been introduced into treatment of LARC after large trials demonstrated excellent long-term oncological outcomes for selected patients (84-86). In this context, the non-operative management (NOM) of LARC patients who have a cCR after neoadjuvant therapy has become a matter of discussion while the appropriate selection of patients for an active surveillance strategy is still challenging (87,88). While the studies supporting TNT had pCR rates of 25–30%, the OPRA trial proposes that organ preservation could be achievable in half of the rectal cancer patients treated with TNT (89). MRgRT could be advantageous for nCRT and TNT due to several reasons (90-92). The role of MRgRT in rectal cancer could be one that enables dose escalation as high doses are needed to achieve higher rates of complete response (93). Given the capabilities in terms of superior soft-tissue contrast, real time imaging and gating using a MR-linac, adaptive boost irradiation could be applicable with smaller margins and higher safety for the surrounding OAR (94). Of course, online adaptation can be valuable, considering the improved visualization of macroscopic tumor. Furthermore, reduction of dose exposure to OAR such as the bladder, the anal sphincter and normal rectal mucosa would be simplified. Differing bladder and rectal fillings have a significant impact on the position of the mesorectum, in particular on the anterior part of the upper mesorectum (95,96). MRgRT with real time imaging has a great potential addressing these challenges. Another innovative approach could potentially be implemented into MRgRT. It has been shown that changes in diffusion weighted imaging (DWI) can predict response to radiotherapy. This information could be used in online adaptation to apply dose escalation to areas with persistent diffusion restriction (97,98).

In a retrospective study, Chiloiro *et al.* reported on a small cohort of 22 patients who received long-course nCRT using MRgRT (99). Five patients (22.7%) had grade 3 GI toxicity. Three patients (15,8%) had a pCR and 6 patients (27,3%) of all analyzed patients had either cCR or pCR. Gani *et al.* published their experience with MR guided boost RT in a 73-year-old patient with a cT3a cN0 cM0 rectal carcinoma, aiming at organ preservation (100). 45 Gy in 25 fractions with a simultaneous integrated boost with 50 Gy in 25 fractions was applied using a conventional linac. Additionally, the patient was prescribed with three boost fractions with 3 Gy per fraction using online adaptive MRgRT on a 1.5 T MR-Linac with 100 cc of ultrasound gel rectally applied to improve target visualization and reduce inter- and intrafractional variability of normal rectal mucosa. There was no grade 2 or higher toxicity. The Dutch group of Intven *et al.* reported on their first experiences on MRgRT in 43 rectal cancer patients, using a 5 fractions short-course concept (5×5 Gy) on a 1.5 T MR-linac (101). Their median in-room time per fraction was 48 minutes with clinically acceptable and well-tolerated adapted treatment plans.

An ongoing trial in the United States led by Frakes *et al.* is looking into MR guided dose-adaptation based on MR morphologic objective measurements during primary chemoradiation (NCT05108428).

The clinical evidence for the use of MRgRT in rectal

cancer is still very scarce. Nevertheless, the potential in the context of dose escalation and organ preservation strategies is promising.

Esophageal cancer

Globally, esophageal cancer is ranked seventh and sixth in terms of cancer incidence and overall mortality, respectively, with approximately 70% of all cases occurring in men and a majority of all cases in less-developed countries (102). Locally advanced esophageal or esophagogastric junctional cancer is typically treated with neoadjuvant chemoradiotherapy followed by an esophagectomy if patients are fit for surgery (103-105). In case of unresectable tumors or unfit patients, definitive chemoradiotherapy is the standard approach (106,107), achieving relatively poor 5-year OS rates between 10% and 35% (108,109).

Historically, the role of diagnostic MRI has been limited in esophageal cancer with computed tomography and endoscopic ultrasound being used for initial staging (110). Approximately one third of the patients who undergo trimodality treatment have a pathological complete response after nCRT (105). With current techniques, however, complete responders cannot be identified reliably (111). In recent years, diffusion-weighted MR imaging has been found to be a prognostic and predictive biomarker when used before and during chemoradiotherapy (112-114). The use of MRgRT in esophageal cancer could allow for smaller target volume margins, resulting in reduced dose exposure to OAR. Dose-escalation could be applied with less toxicity and online adaptive planning would enable radiation oncologists to react to anatomical changes and tumor volume regression. The aspect of intrafraction motion due to respiratory cycles could well be addressed by real time imaging and gated beam delivery (115). A dosimetric study by Lee *et al.* investigated whether MR-linac plans with smaller margins due to maximum-inhalation breath hold (MIBH) could decrease doses to the heart compared to 4-dimensional CT-based plans in ten patients with locally advanced adenocarcinoma of the gastroesophageal junction (GEJ) (116). Mean PTV volume was significantly smaller on the MR-linac plans (689 *vs.* 1,275 cm^3, P<0.01). Mean dose to the heart was significantly reduced in the MR-linac plans with 20.9 *vs.* 27.8 Gy. Significant reductions were also reported for all cardiac substructures. Boekhoff *et al.* started a R-Ideal stage 1b/2a study to gain experience in the implementation of online adaptive MRgRT using a 1.5 T MR-linac in the treatment of esophageal cancer (117). They treated nine patients with chemoradiation with a total of 183 (86%) of 212 fractions successfully delivered on the MR-linac. Main reasons for rescheduling on a conventional linac was discomfort (n=13), MR-linac downtime (n=10) or logistical reasons (n=3). The median MRgRT fraction time was 53 min. Compared to conventional plans, mean lung and heart dose were reduced 26% and 12% in daily adapted MR-linac plans. The authors conclude that MRgRT was only moderately feasible for this patient group, mainly due to the long treatment times. To our knowledge, there are no more published data on clinical trials implementing MRgRT in this tumor entity. Therefore, future studies will have to focus on improvements in the workflow as MRgRT seems to be an interesting option regarding hypofractionation and implementation of functional imaging.

Conclusions

In summary, MRgRT represents an innovative new tool, that enables radiation oncologists to significantly enhance treatment opportunities in a variety of tumor sites. Radiation therapy is more individualized and more precisely tailored to every single treatment situation due to its online adaptation capabilities, which pave the way into a new era in radiotherapy. As MR-linacs are implemented in more and more institutions worldwide, clinical trials will have to generate the evidence, that is needed to clarify the future role of MRgRT. With regard to gastrointestinal tumor diseases, obviously this is one of the anatomical areas where MRgRT has the most benefit compared to conventional CT-based linacs. Functional imaging as response assessment during treatment is potentially going to become another disruptive feature of adaptive radiotherapy. This review clearly focusses on GI primary tumors, but we believe that MRgRT is also a very suitable tool for treatment of abdominal and pelvic oligometastatic disease. On the other hand, online-adaptive workflows are more time-consuming and staff-intensive compared to conventional non-adaptive treatment strategies, which is mainly due to several additional steps such as re-countouring, online plan adaptation and decreased beam on duty cycle when treating moving targets. As for now, the technology of MRgRT itself is still quite expensive. Patient-specific issues include claustrophobia due to generally smaller bore diameters compared to conventional linacs and potential contra-indications for MRI such as incompatible pacemakers or implants made of ferromagnetic materials.

Therefore, future studies will also have to show that the

investments into MR guided therapies make sense in overall health economic terms.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Falk Roeder and Thomas Brunner) for the series "Precision Radiation Oncology in GI Cancers" published in *Journal of Gastrointestinal Oncology*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-961/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-961/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-961/coif). The series "Precision Radiation Oncology in GI Cancers" was commissioned by the editorial office without any funding or sponsorship. J.H.R. reports speaker fees from ViewRay Inc. and travel reimbursement from ViewRay Inc., IntraOP Medical Systems and Elekta Instrument outside the submitted work. J.H.R. further reports a research grant from IntraOP Medical and Varian Medical Systems outside the submitted work. S.A.K. reports research grants from Viewray Inc. and speaker fees from IBA Dosimetry outside the submitted work. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Ristau J, Hörner-Rieber J, Körber SA. MR-linac based radiation therapy in gastrointestinal cancers: a narrative review. J Gastrointest Oncol 2024;15(4):1893-1907. doi: 10.21037/jgo-22-961

