MR-Guided Radiation Therapy for Oligometastatic Malignancies

Description

This review article describes technical advantages for MR-guided radiation therapy (MRgRT) that lead to the rationale for use in the oligometastatic setting. The authors summarize existing data demonstrating the feasibility, safety, and efficacy of MRgRT for various disease sites. Finally, the authors discuss ongoing clinical trials utilizing MRgRT, which will continue to define and expand its role.

Learning Objectives

Upon completing this activity, the readers should be able to:

- understand the evolving treatment of oligometastatic disease and the role of stereotactic body radiation therapy (SBRT) across anatomical disease sites;
- comprehend the pros/cons of MRgRT in the treatment of oligometastatic disease across anatomical disease sites; and
- implement the treatment of oligometastatic disease with SBRT with appropriate understanding of the potential benefits/pitfalls of MRgRT vs. CT-based radiation therapy.

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Target Audience

- Radiation Oncologists
- Related Oncology Professionals

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A considerable body of evidence is emerging to support the existence of an oligometastatic state, in which patients with limited metastases may experience prolonged overall survival (OS),[1] blurring the line between a localized disease state and what was previously considered incurable metastatic cancer. Recent clinical trials demonstrate the benefit of stereotactic body radiation therapy (SBRT) for patients with oligometastatic cancer, typically defined as 1-5 metastatic lesions. Randomized phase II studies of oligometastatic non-small cell lung cancer (NSCLC)[2] and prostate cancer[3,4] showed improved outcomes with SBRT to all metastatic sites. The SABR-COMET study was a phase II trial of patients with up to 5 sites of metastatic disease of various histologies, in which SBRT improved OS and progression-free survival (PFS) as compared to standard palliative therapy.[5]

The promising results of these trials have spawned further trials evaluating SBRT for oligometastatic disease. The NRG has opened phase II/III trials investigating SBRT for patients with oligometastatic breast cancer (BR-002; NCT02364557) and NSCLC (LU-002; NCT03137771). SABR-COMET-10 (NCT03721341) is an ongoing phase III trial investigating the benefit of SBRT for patients with 4 to 10 metastases,[6] potentially expanding the definition of oligometastatic cancer. A search of the national clinical trials database [clinicaltrials.gov] for the term "oligometastatic" reveals 182 studies either active or completed without results, as of the time of this writing. Clearly, there is prominent interest in this paradigm, with large cooperative groups bringing the concept to the international stage.

While the utilization of SBRT for oligometastatic disease is gaining prominence, the potential toxicity should be carefully considered. In the recently published NRG BR-001 trial in which patients with oligometastatic cancer received SBRT to all sites of metastatic disease, the rate of late grade ≥ 3 toxicity was 20% at 2 years.[7] Similarly, the authors of SABR-COMET reported a 29% rate of grade ≥ 2 toxicity in the SABR arm (including 3 treatment-related deaths), compared with 9% in the control arm. Studies of SBRT for central NSCLC tumors also bring to attention the potential for severe treatment-related toxicity.[8,9] Therefore, the potential toxicity associated with delivering SBRT to multiple sites necessitates caution to ensure the burden of late toxicity is minimized, especially in this population who may experience prolonged survival.

With accumulating evidence supporting the use of SBRT in oligometastatic disease, there is increasing interest toward leveraging technologies such as MR-guided radiation therapy (MRgRT) for this purpose. In the context of adaptive SBRT or hypofractionated radiation therapy, the use of MRI guidance has been labeled stereotactic MR-guided adaptive radiation therapy (SMART). SMART represents a novel modality for SBRT delivery in the oligometastatic setting to improve therapeutic efficacy and safety, especially in anatomically constrained sites or in patients who may require SBRT to multiple sites. Early evidence supports the safety and feasibility of utilizing MRgRT (and/

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or SMART),[10] and it is being implemented into clinical practice at many centers. These findings have served as the basis for ongoing prospective trials utilizing MRgRT/SMART. In this review, we will discuss the rationale for SMART in the treatment of oligometastases and summarize existing literature describing its use in various disease sites. Finally, we will discuss the future of SMART and ongoing prospective clinical trials evaluating this treatment paradigm.

Rationale for MRgRT

While achieving increased biologically effective dose (BED)[11] may improve tumor control probability (TCP), dose constraints for organs at risk (OARs) may limit the dose that can safely be delivered.[12] Thanks to enhanced soft-tissue imaging resolution, workflows allowing for efficient online daily adaptive re-planning and real-time tumor tracking, MRgRT has distinct advantages compared with conventional radiation therapy technologies in the delivery of SBRT. Of note, real-time adaptive radiation therapy (RTT) may be achieved in different ways depending on the type of MR-linac utilized. For example, daily adaptive replanning on MRIdian (ViewRay) differs from Elekta Unity's "adapt-to-position" or "adapt-to-shape" approach. The "adapt-to-position" allows for repositioning of the isocenter for better target coverage during daily set-up while "adapt-to-shape" is a tool that automatically propagates contours onto the online planning MRI and can be edited with electron densities (ED) being assigned based on the average ED value of the corresponding contour on the pre-treatment CT.[13] In comparison, the MRIdian system utilizes a couch with 3 degrees of freedom to position anatomy and tumor appropriately with online adaptive therapy focused on tumor/anatomical changes to ensure target coverage and decreased dose to OARs.[14]

One aspect complicating delivery of SBRT is the uncertainty in OAR location due to daily variation in position and filling[15-17] as well as uncertainty of target location due to respiratory motion. While the use of image-guided radiation therapy with cone-beam commuted tomography (CT) provides localization of soft-tissue anatomy and is commonly utilized prior to each SBRT fraction in conventional linac-based delivery, most workflows do not allow for daily plan adaptation. The enhanced imaging visualization with MRI guidance and workflow for many available MRgRT platforms allows for daily online adaptive re-planning, in which target volumes and OARs are recontoured and a reoptimized dose distribution is generated based on the day's anatomy,[18-20] which thus may facilitate dose escalation.[21] Further, variation in target location due to respiratory motion necessitates the use of motion management strategies for SBRT. The use of RTT with gated treatment delivery with MRgRT in some MR-linac systems allows for smaller PTV margins and may be advantageous over other commonly used motion management strategies such as use of internal target volumes (ITVs), which increase the size of the target volume and may lead to difficulty in achieving dose escalation. Further advantages of MRgRT over CT-based SBRT include improved soft-tissue visualization for precise delineation of target and normal tissues on both planning and daily imaging. Serial MRI imaging during treatment may also provide insight into treatment response.

Overview of Evidence for Site-Specific MRgRT

Abdomen and Retroperitoneum

Common targets for SBRT in the abdomen include primary and metastatic tumors of the liver, pancreas, adrenal glands, kidney, and lymph nodes. OARs including the stomach, duodenum, small bowel, and uninvolved liver are radiosensitive organs subject to positional uncertainty due to respiratory motion and variable daily filling. Therefore, abdominal oligometastases represent an ideal setting for MRgRT and SMART and available data support excellent clinical outcomes with low rates of radiation-therapy-related toxicity.

The MOMENTUM study is a multi-institutional prospective registry conducted by the MRI Linac Consortium, enrolling patients treated with high-field (1.5 Tesla) MRgRT to a variety of disease sites.[22] In MOMENTUM, 17% of liver, 76% of pancreas, 70% of rectum, and 82% of lymph node fractions were treated with online adaptation, and the rate of grade ≥ 3+ acute toxicity was only 4%. A phase I trial including 20 patients with oligometastatic or unresectable primary intra-abdominal tumors treated with SBRT demonstrates the importance of the SMART approach in this setting, where adaptive plans were created for 81 of 97 fractions and in which PTV coverage was increased in 64 of 97 fractions.[23] Of the 81 adapted fractions, 75% were adapted primarily because the initial plan violated OAR dose constraints. Notably, the authors reported 0% grade ≥ 3 acute toxicity. Authors from the University of California, Los Angeles (UCLA), published their institutional experience of 106 patients treated with SMART to abdominal or pelvic primary or oligometastatic tumors to a median dose of 40 Gy in 5 fractions. In contrast to MOMENTUM and Henke et al, only 13.9% of the UCLA fractions were adapted. The 2-year local control was 74%, including 96% with those achieving BED >100 Gy vs 69% for BED < 100 Gy, while < 1% experienced grade 3+ acute toxicity and 7.3% experienced late grade 3+ late toxicity.[24]

For liver and hepatobiliary lesions specifically, MRgRT is associated with excellent local control and low

TABLE 1. LIST OF ONGOING US CLINICAL TRIALS FOR MR-GUIDED RADIATION THERAPY (CONTINUED ON PAGE 28)

Study Title	Sponsor	Condition/Disease	URL
SMART-ONE: Stereotactic MRI-guided Adaptive Radiation Therapy (SMART) in One Fraction	Baptist Health South Florida	Oligometastatic cancer, up to 10 sites of disease	https://clinicaltrials.gov/ct2/show/NCT04939246
Real-Time MRI-Guided 3-Fraction Accelerated Partial Breast Irradiation in Early Breast Cancer	University of Wisconsin, Madison	Breast cancer DCIS LCIS	https://ClinicalTrials.gov/show/NCT03936478
CONFIRM: Magnetic Resonance Guided Radiation Therapy	Dana-Farber Cancer Institute	Gastric cancer Invasive breast cancer In situ breast cancer	https://ClinicalTrials.gov/show/NCT04368702
Pilot Study of Same-Session MR-Only Simulation and Treatment with Stereotactic MRI-guided Adaptive Radiotherapy (SMART) for Oligometastases of the Spine	Washington University School of Medicine	Oligometastases of the spine	https://clinicaltrials.gov/ct2/show/NCT03878485
Stereotactic MRI-Guided On-table Adaptive Radiation Therapy (SMART) for Locally Advanced Pancreatic Cancer	ViewRay	Pancreatic cancer	https://clinicaltrials.gov/ct2/show/NCT03621644
MRI-Guided Adaptive RadioTHerapy for Reducing XerostomiA in Head and Neck Cancer (MARTHA-trial)	Panagiotis Balermpas, University of Zurich	Head and neck cancer Xerostomia due to radiation therapy	https://clinicaltrials.gov/ct2/show/NCT03972072
Three Fraction Accelerated Partial Breast Irradiation as the Sole Method of Radiation Therapy for Low-Risk Stage 0 and I Breast Carcinoma	Washington University School of Medicine	Breast carcinoma Breast cancer	https://clinicaltrials.gov/ct2/show/NCT03612648
Stereotactic MR-Guided Radiation Therapy	Dana-Farber Cancer Institute	Pancreas cancer Lung cancer Renal cancer	https://clinicaltrials.gov/ct2/show/NCT04115254

Key: DCIS = ductal carcinoma in situ, LCIS = lobular carcinoma in situ, PET = positron emission tomography, CT = computed tomography, SBRT = stereotactic body radiation therapy

rates of toxicity. A systematic review of 16 studies including 973 patients with 1034 liver lesions treated with MRgRT demonstrated local control rates of 93% at 3 years with a 5.3% risk of grade 3 or higher toxicity.[25] Similarly, in a multi-institutional retrospective study of 26 patients with unresectable primary or metastatic liver tumors treated with MRgRT, freedom from local progression (FFLP) at 21 months was 80.4% overall, including 100% for hepatocellular carcinoma vs 75% for colorectal metastases. This excellent local control was accompanied by minimal toxicity, as only 7.7% of patients developed late grade 3 gastrointestinal (GI) toxicity and no patient had grade 4 or 5 GI toxicity.[26] Luterstein et al published the UCLA experience of MRgRT for 17 patients with locally advanced cholangiocarcinoma. The 2-year local control was 73.3%, and only 1 patient (6%) experienced late grade 3 toxicity.[27]

While there is no defined standard of care for patients with locally advanced or borderline resectable pancreatic cancer, SBRT has emerged as an improvement over conventionally fractionated regimens.[28] Given close proximity to radiosensitive intra-abdominal structures, the rate of severe toxicity with pancreas SBRT approaches 10%.[29] In a phase I trial of 20 patients with inoperable pancreatic cancer treated with MRgRT to 24 Gy in 3 fractions, no patient experienced grade 3+ toxicity.[30] Rudra et al described a series of 44 patients with unresectable pancreatic cancer treated with conventionally fractionated radiation therapy, hypofractionated radiation therapy, or SBRT with an MRgRT approach and demonstrated that patients with BED >70 Gy were associated with improved OS with a nonsignificant trend toward improved local control (77% vs 57%), with only 3 patients experiencing grade 3+ toxicity.[31] Chuong et al from Miami Cancer Institute reported their institutional experience with MRgRT for 35 patients with pancreatic cancer treated with MRgRT to a median dose of 50 Gy in 5 fractions with 1 year local control of 87.8% and risk of late grade 3 toxicity of 2.9%.[32] Similarly, the application of SMART for reirradiation for recurrent pancreatic cancer is being explored.[33]

Given proximity to critical organs (eg, stomach, bowel), adrenal and renal tumors also represent promising targets for SMART. In a multi-institu-

TABLE 1. LIST OF ONGOING US CLINICAL TRIALS FOR MR-GUIDED RADIATION THERAPY (CONTINUED FROM PAGE 27)

Study Title	Sponsor	Condition/Disease	URL
Stereotactic Body Radiotherapy and Focal Adhesion Kinase Inhibitor in Advanced Pancreas Adenocarcinoma	Washington University School of Medicine	Pancreas cancer	https://clinicaltrials.gov/ct2/show/NCT04331041
Nivolumab, Ipilimumab and Chemoradiation in Treating Patients With Locally Advanced Pancreatic Cancer	Herlev Hospital	Locally advanced pancreatic cancer	https://clinicaltrials.gov/ct2/show/NCT04247165
Study of PSMA PET/MR-Guided Stereotactic Body Radiation Therapy With Simultaneous Integrated Boost (SBRT-SIB) for High-Intermediate and High Risk Prostate Cancer	Weill Medical College of Cornell University	Prostate cancer	https://clinicaltrials.gov/ct2/show/NCT04402151
CT-Guided Stereotactic Body Radiation Therapy and MRI-guided Stereotactic Body Radiation Therapy for Prostate Cancer, MIRAGE Study	Jonsson Comprehensive Cancer Center	Prostate adenocarcinoma	https://clinicaltrials.gov/ct2/show/NCT04384770
Adaptative MR-Guided Stereotactic Body Radiotherapy of Liver Tumors	Centre Georges Francois Leclerc	Liver cancer	https://clinicaltrials.gov/ct2/show/NCT04242342
Preoperative MR-Guided Radiation Therapy in Gastric Cancer	Washington University School of Medicine	Gastric adenocarcinoma	https://clinicaltrials.gov/ct2/show/NCT04162665
Immune Checkpoint Inhibitor and MR-guided SBRT for Limited Progressive Metastatic Carcinoma	Baptist Health South Florida	Metastatic carcinoma	https://clinicaltrials.gov/ct2/show/NCT04376502
Randomized Phase II Trial of Salvage Radiotherapy for Prostate Cancer in 4 weeks v. 2 weeks	Weill Medical College of Cornell University	Prostate cancer	https://clinicaltrials.gov/ct2/show/NCT04422132

Key: DCIS = ductal carcinoma in situ, LCIS = lobular carcinoma in situ, PET = positron emission tomography, CT = computed tomography, SBRT = stereotactic body radiation therapy

tional retrospective study including 13 metastatic adrenal lesions treated with RTT radiation therapy with gold fiducial markers and 8 adrenal lesions treated with conventional linac-based SBRT without RTT, no grade 2 or higher reactions were reported for either group. However, the group treated with RTT had 100% local control at 1 year, compared with 50% local control in the group treated without RTT, highlighting the importance of accounting for tumor motion and pointing toward the potential utility of MRgRT in this setting. Similarly, Palacios et al published an institutional experience of patients treated with MRgRT for adrenal tumors at VU Medical Center in Amsterdam, Netherlands. They noted significant daily positional variation for bowel, duodenum, and stomach, resulting in up to one-third of baseline plans not meeting dose constraints for each fraction. Further, they noted that online reoptimization improved target coverage in 63% of fractions. Similarly, emerging data support the feasibility and utility of SMART for primary or secondary kidney tumors[34-37] with a similar rationale to that for adrenal tumors.

Pelvis

Pelvic SBRT is most frequently utilized for prostate tumors and pelvic lymph node recurrences. Radiosensitive intrapelvic organs (ie, bladder, rectum, small bowel) are subject to daily variation in location and filling, making this an ideal setting for MRgRT. The use of hypofractionated radiation therapy and SBRT is increasingly being utilized and now represents a standard-of-care option for localized prostate cancer.[38] While high-quality evidence supports the use of prostate SBRT, there is concern for potentially increasing the risk of urinary and GI toxicity compared with conventionally fractionated regimens,[39-42] leading to interest in utilization of MRgRT in this context. The benefit of MRgRT for prostate cancer lies in the ability to account for daily variation in bladder and rectal filling as well as RTT of the prostate,[43] and the ability to treat without implanted fiducial markers. A prospective single-arm phase II trial of 101 patients treated with SMART to 36.25 Gy in 5 fractions over 2 weeks with daily adaptation

demonstrated minimal GI and genitourinary (GU) toxicity.[44,45] Similarly, 25 patients treated with SMART to 35 Gy in 5 fractions on a prospective observational protocol had only 12% grade 2 GU toxicity and no grade 3 toxicity.[46] Although SMART may be helpful for prostate SBRT, much of the benefit may be derived from RTT and gating secondary to bowel/bladder changes. This was most recently seen in a nonadaptive, MR-guided prostate SBRT series by our group showing minimal toxicity and excellent PSA (prostate-specific antigen) response.[47] Treating the primary tumor (as well as limited sites of spread) in the setting of oligometastatic prostate cancer may significantly improve patient outcomes and quality of life.[48] Additionally, the broad published experience of prostate SBRT can inform the utilization of MRgRT for pelvic nodal oligometastases and oligorecurrences as directed by newer imaging agents such as prostate-specific membrane antigen (PSMA) to improve the early detection of oligometastatic disease. As many pelvic malignancies such as prostate cancer, bladder cancer, rectal cancer, and gynecologic cancers are managed primarily with radiation therapy, treatment of recurrent pelvic lymph node metastases in the re-irradiation setting presents a challenging clinical scenario that might be ideally addressed with MRgRT. Small retrospective series have demonstrated the feasibility of the SMART workflow for pelvic nodal metastases, in which online adaptive replanning may decrease the dose to OARs and facilitate the use of smaller margins[49,50,51] for definitive management of pelvic oligometastatic disease.

Thorax

SBRT is the standard of care for early stage, unresectable or medically inoperable NSCLC. Outcomes with SBRT have demonstrated excellent local control with limited toxicity for peripheral lesions with 1-,[52,53] 3-[54-57]or 5-[58] fraction SBRT regimens. However, the potential for severe or life-threatening toxicity associated with SBRT to central or ultracentral lung tumors, necessitates caution.[59-62] The most recent example of this is the Nordic-HILUS trial. HILUS is a prospective, single-arm phase 2 trial including 65 patients with ultracentral lung tumors (defined as within < 1cm of the proximal bronchial tree without endobronchial invasion)[63] treated with 7 Gy x 8 fractions in which 15% of patients experienced treatment-related death (grade 5 toxicity). In total, the rate of grade 3 to 5 toxicity in HILUS was 34%.[64] These sobering results illustrate that even with modern dose constraints and treatment planning techniques, the potential for grave toxicity remains for ultracentral lung tumors. Opposing this concern for toxicity is the understanding that dose-escalation is often required for durable control in NSCLC, with patients achieving BED >100 Gy associated with improved OS.[65] Due to the necessity for dose-escalation and the high risk of severe toxicity, SBRT for ultracentral tumors should optimally be delivered with appropriate motion management strategies to treat with the smallest possible margin. Due to respiratory motion, the use of ITVs with 4D CT is often utilized to ensure accurate localization.

Early experiences with MRgRT show promise for treatment of central lung tumors. In a small phase I trial, 5 patients with oligometastatic or unresectable primary ultracentral thorax tumors received MRgRT to 50 Gy in 5 fractions. Four of 5 patients and 10 of 25 total fractions were planned with daily online adaptation. No patients had grade ≥ 3 acute toxicity while 2 patients had late grade 3 or 4 toxicity. In a phase II clinical trial in which 41 patients with central lung tumors received SBRT, the rate of grade ≥ 3 toxicity was 14.6%, including 1 case of fatal hemoptysis.[66] A retrospective series of 50 patients with 54 primary or metastatic lung tumors treated with SMART showed excellent outcomes, where 93% were able to achieve BED >100 Gy, and grade 3 toxicity was seen in only 8% without any grade 4 or 5 toxicity.[67] In a separate series of 25 patients with central lung tumors treated with SMART to 60 Gy in 8 fractions or 55 Gy in 5 fractions, Finazzi et al illustrated the benefit of daily adaptation, as PTV coverage was improved in 61% of fractions and reduced the number of OAR constraint violations.[66] Thus, patients with central or ultracentral lung tumors may be ideal for treatment with MRgRT, in which gated delivery with RTT can avoid the use of larger ITVs[68] and optimize dose-escalation, and should be tested in prospective trials (NCT 04917224). MRgRT could have important implications for the treatment of both primary and metastatic lesions to the lung to allow for dose escalation with decreasing the risk of toxicity.

With evidence pointing to the effectiveness of single-fraction SBRT for peripheral lung tumors,[51,70] there has also been interest in adopting MRgRT for this approach. Finazzi et al reported a series of 23 patients with peripheral lung tumors treated with SMART with breath-hold gated delivery. The SMART-PTVs were estimated to be less than 54% of the volume of ITVs generated for the same tumor, while adaptation facilitated improved PTV coverage and allowed all patients to achieve BED >100 Gy. Only 1patient experienced grade 3 toxicity, and there were no cases of grade 4 or 5 toxicity.[69]

The Future of MR-Guided Radiation Therapy: Ongoing Clinical Trials

A number of ongoing clinical trials are evaluating the use of MRgRT in the management of primary or oligometastatic disease. Notably, the

SMART-ONE trial, which will open at the Miami Cancer Institute, is a single-arm trial investigating the feasibility of delivering single-fraction, MR-guided SBRT to up to 10 disease sites (NCT04939246). Additional active clinical trials include patients being treated with MRgRT for breast, prostate, pancreas, liver, and spine tumors, among others **(Table 1)**. Isotoxic dose escalation has potential to improve local control and may even impact OS; early reports are encouraging but this needs to be tested in prospective trials.[53,71] As of yet, no prospective comparisons have been reported to determine the benefit of MRgRT over CT-based SBRT. As evidence begins to accumulate supporting the feasibility of MRgRT for various disease sites, direct comparison with CT-based SBRT will be necessary to optimize patient selection for this advanced treatment modality. MRgRT also has potential to incorporate diffusion-weighted (DWI) imaging into its daily scans to assess for intra-treatment tumor changes before tumor size or morphology changes appear on traditional imaging methods.[72]

Barriers and Limitations of MR-Guided Radiation Therapy

While the use of MRgRT is growing, broad adoption is limited by cost, availability, practical factors, and technical aspects. Commissioning, treatment delivery, and maintenance of MR-linac systems are resource intensive, requiring multidisciplinary cooperation and expertise from physicists, therapists, dosimetrists, and physicians.[73] The use of MR systems also requires standardized MRI safety protocols in addition to typical radiation safety protocols, and staff must be appropriately trained to ensure safety for all involved. The use of online adaptation with MRgRT may require up to 45-120 minutes of total treatment time, requiring extended physician and physicist presence at the machine. Patients must be able to tolerate appropriate positioning and immobilization, and potential anxiety or claustrophobia must be managed proactively. In patients with oligometastatic disease who may receive MRgRT or SMART to multiple sites, this lengthy treatment time may be multiplied. Physical limitations of MRgRT may include Lorentz forces, which may potentially lead to overdosing hollow organs; MRI geometric distortion; uncertainty associated with MRI to radiation isocenter distance; multileaf collimator position error; and uncertainties with voxel size and tracking.[26] Similarly, the lack of electron density and attenuation coefficient information on MRI requires fusion to CT images for dose-calculations in treatment planning. Due to these additional technical factors, physicist and dosimetrist experience and expertise with these issues is essential to ensure appropriate treatment planning and delivery.

Conclusion

MRgRT represents a promising treatment modality for patients with oligometastases. An accumulating body of evidence supports the feasibility of MRgRT and SMART for various disease sites. Thanks to enhanced soft-tissue resolution and workflows allowing for daily online-adaptation and RTT, MRgRT can facilitate dose-escalation to optimize TCP and minimize normal tissue complication probability. Ongoing clinical trials will continue to define and potentially expand the role of MRgRT for primary and oligometastatic disease.

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