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Magnetic Resonance Image-Guided Radiotherapy (MRIgRT): a 4.5-Year Clinical Experience

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Abstract

AIMS—Magnetic resonance image-guided radiotherapy (MRIgRT) has been clinically implemented since 2014. This technology offers improved soft-tissue visualisation, daily imaging, and intra-fraction real-time imaging without added radiation exposure, and the opportunity for adaptive radiotherapy (ART) to adjust for anatomical changes. Here we share the longest single-institution experience with MRIgRT, focusing on trends and changes in use over the past 4.5 years.

MATERIALS AND METHODS—We analysed clinical information, including patient demographics, treatment dates, disease sites, dose/fractionation, and clinical trial enrolment for all patients treated at our institution using MRIgRT on a commercially available, integrated 0.35 T MRI, tricobalt-60 device from 2014 to 2018. For each patient, factors including disease site, clinical rationale for MRIgRT use, use of ART, and proportion of fractions adapted were summated and compared between individual years of use (2014–2018) to identify shifts in institutional practice patterns.

RESULTS—Six hundred and forty-two patients were treated with 666 unique treatment courses using MRIgRT at our institution between 2014 and 2018. Breast cancer was the most common disease, with use of cine MRI gating being a particularly important indication, followed by abdominal sites, where the need for cine gating and use of ART drove MRIgRT use. One hundred and ninety patients were treated using ART in 1,550 fractions, 67.6% (1,050) of which were adapted. ART was primarily used in cancers of the abdomen. Over time, breast and gastrointestinal

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cancers became increasingly dominant for MRIGRT use, hypofractionated treatment courses became more popular, and gastrointestinal cancers became the principal focus of ART.

DISCUSSION—MRIGRT is widely applicable within the field of radiation oncology and new clinical uses continue to emerge. At our institution to date, applications such as ART for gastrointestinal cancers and accelerated partial breast irradiation (APBI) for breast cancer have become dominant indications, although this is likely to continue to evolve.

Keywords

MRIGRT; online-adaptive radiation therapy; ART; MRI-guided radiation therapy; SMART

INTRODUCTION

Magnetic resonance image-guided radiotherapy (MRIGRT) has long been sought within the field of radiation oncology. MRIGRT offers superior daily visualisation of soft-tissue disease sites for improved set-up accuracy, daily imaging of sufficient quality for online adaptive radiotherapy (ART), and the potential for real-time target-based cine MRI (cMRI) gating for intra-fraction motion management without additional radiation exposure to patients [1–4]. Over the past two decades, advances in the integration of MRI and radiotherapy devices culminated in the clinical implementation of MRIGRT at our clinic in 2014 [5].

Since its initial implementation, MRIGRT use has expanded to multiple centres and countries. In our clinic, it has quickly become an integral treatment modality, and has been the focus of several prospective clinical trials and multi-institutional studies [4,6,7]. As the field acclimatises to the availability of MRIGRT, clinical use of this technology matures and new applications continuously emerge.

Previously, we described our early institutional experience with MRIGRT [8]; however, as familiarity with the technology is gained, use is honed to derive maximal therapeutic benefit. In this work, we present the longest single-institution clinical experience using MRIGRT. The goal of this paper is to describe our 4.5 years of use, including shifts in our practice patterns over time, to guide best clinical practice as MRIGRT gains traction in the global clinic.

MATERIALS AND METHODS

Setting and Patients

The Radiation Oncology department at Washington University in St Louis includes 21 disease-site-specific attending radiation oncologists who cover our main site as well as five satellite facilities. Our main facility is equipped with eight linear accelerators (linacs) including the Edge radiosurgery system, an MRI-guided linac (completing commissioning), and the Halcyon, in addition to a Leksell Gamma Knife ICON, a cobalt-60-based MRIGRT system, a single-gantry proton therapy system, and a full brachytherapy suite. All patients included in this study were treated with MRIGRT between 2014–2018 and were either part of prospective clinical protocols (institutional protocol nos. 201410002, 201401160, 201311081, 201611018, 201510101, 201412038), a prospective MRIGRT patient registry

(registry no. 2013111222), or an institutional retrospective registry (registry no. 201301149). The dataset was interrogated to obtain clinical information, including demographic information, dates of treatment, disease site treated, dose and fractionation, and clinical trial enrolment. For each patient, the primary clinical rationale for the use of MRIGRT was evaluated (adaptive treatment, cine gating, daily MRI for improved setup accuracy). For patients receiving ART, we also examined the proportion of fractions adapted. These factors were then summated and compared between individual years of use (2014–2018) to identify shifts in institutional practice patterns.

Three clinical MRIGRT systems are commercially available and have been clinically used including a 0.35 T MRI-linac, an integrated 0.35 T-tri-Co-60 device, and a 1.5 T MRI-linac system [5,9,10]. The patients included in this experience were treated using the 0.35 T-tri-Co-60 system, although our clinic is commissioning its counterpart, the 0.35 T MRI-linac device. Detailed descriptions of the 0.35 T MRIGRT system, commissioning, quality assurance, and the imaging unit have been published [5,11,12]. In summary, the MRIGRT system is comprised of a tri-cobalt-60 radiation delivery device straddled by an open split-solenoid low-field (0.35 T) magnetic resonance imaging (MRI) device with a nominal dose rate of 550 cGy/min from three 27.3×27.3 cm² fields to the 105 cm isocentre [5].

Simulation, Planning, and Treatment Delivery

All patients treated with MRIGRT underwent computed tomography (CT) simulation and an MR simulation; details for multiple simulation and treatment techniques have been described [4,8,13]. Patient positioning during CT simulation was determined by the treating physician and emulated the position used during MRIGRT. Following simulation, CT and MR simulation images are transferred to an independent treatment planning system (TPS) for volume delineation. These images are then transferred to the MRIGRT dedicated TPS for plan creation. The dedicated TPS uses a Monte Carlo dose calculation algorithm and is capable of creating both conformal and intensity modulated radiation therapy (IMRT) plans [14]. Details on plan delivery including cine gating and ART planning and delivery workflows have been reported previously [2–4].

Statistical Analysis

Data analyses were performed using Excel 2013 (Microsoft Corporation, Redmond, WA, USA).

RESULTS

Patient Characteristics and Disease Sites

Between January 2014 and March 2018, 642 patients with a median age of 64 years (range 64–90 years) were treated with 666 unique courses of MRIGRT. This included 240 IMRT, 266 stereotactic body radiation therapy (SBRT), and 160 three-dimensional (3D) conformal plans delivered over a total of 7,884 fractions. The median number of fractions per patient was 10 (mean 12; range 1–44) with a median dose per fraction of 450 cGy (range 115–2,000 cGy). Disease sites included the abdomen in 41.2%, breast in 31.4%, thorax in 11.6%, head and neck/central nervous system (CNS) in 2.6%, and pelvis in 13.2% of cases (Table 1,

Figure 1). Of the abdominal malignancies treated, pancreatic and hepatobiliary primaries comprised the majority of patients (15.2% and 13%, respectively). Breast cancer treatment courses included accelerated partial breast irradiation (APBI; 30.5%) and whole-breast radiation (1%).

Rationale for MRIGRT

Physician rationale for use of MRIGRT was variable, but could be stratified into three principal reasons: (1) improved soft-tissue visualisation for set-up accuracy in 93 patients (14%); (2) cMRI gating for intra-fraction motion management in 383 patients (57.5%); and (3) online and offline ART in 190 patients (28.5%). Figure 2 provides a visual summary of these rationales. MRI visualisation and set-up was primarily used in the treatment of pelvic malignancies (65 patients), including prostate and bladder malignancies. Breast cancer was the most common disease treated over the total 4.5 years due to the advantage of cMRI gating, comprising the majority of treatment courses delivered (206 patients), followed by abdominal (98 patients) and thoracic (66 patients) malignancies. For APBI patients in particular, MRIGRT was selected for the advantage of planning target volume (PTV) reduction enabled by MRI localisation and cine gating upon the lumpectomy cavity [13]. Of the 190 patients who received ART, the vast majority (169/190) had abdominal malignancies (Figure 3). This included 91 pancreas and 39 hepatobiliary patients. A large proportion of patients were treated as part of prospective clinical protocols (XX%). Table 2 provides a summary of key institutional protocols completed or currently accruing at our institution, as well as the clinical rationale or study hypothesis for benefit of MRIGRT for each protocol.

Treatment Trends

Between 2014 and 2018, the proportion of abdominal patients increased steadily from 24.4% to 60%. An increase in the proportion of breast malignancies treated was also observed over this time frame (21% in 2014 versus 30% in 2018). Concomitantly, we observed a decrease in the annual proportion of treated patients who had thoracic or pelvic malignancies. Figure 1b illustrates the proportion of treatments that each disease site contributed, per year. We also noted that the average number of fractions used per treatment course decreased steadily over time, from 17.2 fractions in 2014 to 7.2 fractions per course in 2018 (average 14 in 2015, 11.7 in 2016, and 9.4 in 2017).

With regards to adaptation, 190/666 total treatment courses were delivered using ART. Of 1,550 fractions delivered to these 190 patients, 67.7% (1,050) of fractions were adapted. Use of ART increased by year, with nine patients undergoing adaptation in 2014, 41 in 2015, 50 in 2016, and 75 in 2017. Abdominal malignancies comprised the largest proportion of ART, and this proportion increased over time (23.3% in 2014 versus 74.8% in 2018; Figure 3). Notably, in patients receiving ART, the average proportion of treatment fractions that were adapted also increased over time, from 0.34 in 2014 to 0.79 in 2018 (0.64 in 2015, 0.72 in 2016, 0.77 in 2017), indicating improved physician selection of cases likely to require daily adaptation (Figure 3).

Of note, our institution has recently installed a 0.35 T MRI-linac. Although we have not initiated patient treatments on this device at the time of submission of this work,

commissioning is nearing completion, and we have begun evaluation of plan qualities between our two MRIGRT devices. In several sites, we have observed increased sharpness of dose gradients as anticipated with a linac compared to a tri-cobalt-60 source (unpublished work), which may increase future use of MRIGRT in disease sites that demand especially steep dose fall-off.

Treatment Outcomes

Although prospective outcomes of treatment using MRIGRT have been and will continue to be reported separately by our institution for the prospective studies conducted (see Table 2), our reported outcomes using this technology have been positive thus far. In the abdomen, we found in a prospective Phase I trial that SMART permits achievement of ablative dose levels (BED = 100 or greater) with zero observed acute or late Grade 3 or higher gastrointestinal (GI) toxicities and no detriment to quality of life [4]. Multi-institutional retrospective data (manuscript in press) for use of MRIGRT in locally advanced pancreatic cancer indicates that use of this technique to achieve similarly escalated BED correlates with improved overall survival [7]. For APBI, use of MRIGRT has allowed achievement of reduced PTV margins due to improved visualisation of the lumpectomy cavity and monitoring of intra-fraction motion [13]. A Phase I trial of single-fraction high-gradient partial breast irradiation has been completed on the basis of this observation, and zero Grade 2 or higher acute toxicities were observed in the preliminary report of outcomes [15]. Early results also indicate zero failures in the treated quadrant and that this technique achieves excellent-to-good cosmetic outcomes (data to be presented at ASTRO 2018), although these long-term outcome results are not fully mature at this time. In summary, MRIGRT has resulted in reduction in toxicity and potential improvements in outcomes in our clinic, consistent with the apparent improvement in the therapeutic index achieved with this technology.

DISCUSSION

Here we present the longest implementation of MRIGRT in the radiation oncology clinic. Our dataset comprises over 650 treatment courses for 642 patients across 4.5 years of use. Specifically, we report changes in patterns of our use of this technology over the past 4.5 years to highlight its key applications and share our experience with an expanding field.

First, we observed that the relative use of MRIGRT across disease sites shifted prominently over the past 4.5 years in our clinic. Initially, our department chose to emphasise smooth integration of the device into our clinic, with broad use across numerous disease sites. Initial use often mimicked standard linear accelerator treatment planning, including use of the device for typical, conventionally fractionated, non-adaptive plans, in order to uncover potential device advantages. Over the last 4.5 years, MRIGRT use for treatment of breast and GI cancers expanded dramatically. For breast, novel applications such as APBI with MR set-up for improved visualisation and cine MR gating on the lumpectomy cavity allowed for reduction of treatment margins from the standard 2–2.5 cm GTV to PTV expansion using conventional EBRT to a total 1 cm expansion with MRIGRT, which matches our brachytherapy APBI margin [13,15]. For GI cancers, the ability to perform online and offline adaptation based on changes in daily tumour and OAR anatomy, as well as cMRI

gating to mitigate the effects of respiratory motion, resulted in substantial increase in use. cMRI gating has particularly affected the workflow for liver SBRT at our institution and others, as SBRT can now be performed without fiducial placement, using gadoxetic acid (Eovist, Bayer HealthCare Pharmaceuticals, USA) contrast medium as needed, and with gating on the tumour volume itself [16].

With regards to adaptive radiotherapy, our use has also shifted over the past 4.5 years. In 2018, as compared with 2014, we adapt more for GI tumours than for any other disease site. As our adaptive use shifted toward a larger proportion of GI cancers, the proportion of fractions adapted per treatment course also shifted closer to 100%, indicating that GI disease sites are the highest yield application for daily adaptation based on inter-fraction changes in tumour and organ-at-risk geometry. In fact, the first ever, prospective clinical trial of stereotactic, MRI-guided adaptive radiotherapy (SMART) focused on GI malignancies [4]. In the midst of our 4.5 year use, we also adopted an institutional guideline that abdominal cases to be considered for adaptation should comprise tumours located within 2 cm of the viscous GI tract, to maximally select patients likely to benefit. Pelvic disease sites, although they were not treated as frequently at our institution in the last 4.5 years, could similarly benefit from adaptation, and are the subject of two prospective trials (one for SMART to ovarian oligometastases and one for prostate SMART) that have recently completed accrual at our site and others [6,17]. In general, online ART addresses a major shortcoming of prior treatment modalities: the ability to ablate lesions safely in the setting of rapidly shifting and unpredictable daily anatomy. As anticipated, adaptation increases the therapeutic index of ART in such settings [4,18], permitting dose escalation that correlates with improved progression-free and overall survival for disease such as locally advanced pancreatic cancer (LAPC) that have historically not clearly benefited from RT [7]. Indeed, the first multi-institutional clinical trial using MRIGRT will focus on LAPC and ask this question prospectively [19]. We also noted an increase in use of hypofractionated treatment courses over the time-frame examined, which may make best use of applications such as ART that are more time-intensive.

Although use of MRIGRT in some sites became less prominent over the past 4.5 years at our institution, such trends may not necessarily imply lack of benefit, but rather need for further technology advancement and more nuanced use. Although analyses have demonstrated that IMRT plans created for the tri-cobalt-60 source are acceptable [14], lung plans for small target volumes such as for SBRT are less conformal using a cobalt-60 device compared to a linac [20]; however, our early institutional analysis indicates that plan quality with the MRI-linac is (as expected) equivalent to CT-based linac plans. Thus, we anticipate that clinical availability of MRI-linac devices will open further use for ART to sites such as the central thorax, where sharp dose gradients are most critical, based on both tumour response and OAR motion [21,22]. Prostate SBRT, which has been implemented with MRIGRT at other institutions with success, will also benefit from sharper dose gradients and is also likely to expand as an indication for MRIGRT [6].

It is critical to note that our experience is not exhaustive; we acknowledge that other centres have developed additional specialised applications and that new treatment and research possibilities continuously emerge. In particular, sarcomas, gastric cancers, and CNS

malignancies are of developing interest, as is use of MRIGRT for unique applications in radiomics [23–26]. Applications for MRIGRT for rectal cancers and head and neck cancers have been explored and are also underway at our institution [27,28]. The unique emergence of SBRT for successful ablation of ventricular tachycardia at our institution also presents an fascinating potential non-malignant MRIGRT application, given the need to precisely account for the motion of the heart from both the cardiac and respiratory cycles [29].

We acknowledge several study limitations. First, all treatments reported were performed using a 0.35 T imaging device, which may impact image quality; however, images are known to be sufficient for ART and are an improvement upon prior cone-beam CT technologies. Although the commercially available 1.5 T system may ultimately produce improved-quality images, it has yet to be widely used clinically. At present, the available 1.5 T device also does not permit cMRI gating, limiting some MRIGRT applications until this technological obstacle is solved. Of note, current 0.35 T devices limit cMRI gating to a single sagittal plane, restricting some intrafraction motion monitoring, but this is sufficient for key applications such as the respiratory cycle. Although new images sequences for the 0.35 T devices, including T1-weighted and T2-weighted pulse and diffusion-weighted imaging (DWI) are under development by the manufacturer, sequence development beyond the standard balanced steady state free precession (bSSFP) sequence was previously institution dependent. This may have slowed implementation and collaborative research in disease sites that are not best imaged with the primary sequence, leading to their under-representation here. Additionally, while we highlight our emerging patterns of best use, prominence of disease types may vary by country and degree of device use in particular disease sites may also be impacted by physician preference. It is plausible that our GI and breast radiation oncologists have pursued use of the device more than other disease sites, resulting in disproportionate use that may be less generalisable to other institutions. Finally, accurate point-dose accumulation, autocontouring, and workflow improvements are areas of active research that may benefit applications such as SMART and reduce demands of cost and time [30,31].

In summary, MRIGRT has a broad range of applications within the field of radiation oncology and new clinical indications continue to emerge. At our institution to date, applications such as ART for GI cancers and APBI for breast cancer have become dominant indications that may best showcase the benefits of available MRIGRT technologies; however, as technology advances and clinical use matures, these trends are likely to continue to evolve.

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Highlights

- Here we report single-institution clinical use patterns of magnetic resonance image-guided radiotherapy (MRIgRT), which has been implemented at our institution since 2014.
- In 4.5 years, 642 patients were treated with 666 unique treatment courses, including 1550 fractions of adaptive radiotherapy (ART).
- Physician rationale for MRIgRT could be stratified into three principle reasons: 1. Improved visualization for setup 2. Cine MR gating 3. Online and offline ART
- Over time, breast and gastrointestinal cancers became the dominant indications for MRIgRT and treatment regimens became increasingly hypofractionated (12 fractions)
- Over 4.5 years of use, gastrointestinal cancers became the principle indication for online ART
- The changes in patterns of use observed here may help guide best clinical use for other institutions beginning implementation of MRIgRT

Figure 1.

Distribution of disease sites treated over 4.5 years based on anatomical sites (a), and annual treatment trends from 2014 to 2018, with the y-axis representing the percentage of patients by year (b).

Figure 2.
Physician rationale for the use of MRIGRT with distribution of disease sites treated.

Figure 3.
Percentage of fractions adapted for patients treated with ART.

Table 1.

Disease sites treated between 2014–2018.

Disease sites treated	N	%
Abdomen		
Oligometastases	59	8.9
Pancreas/duodenum	101	15.2
Hepatobiliary	87	13.1
Gastric	15	2.3
Sarcoma	7	1.1
Other	6	0.9
Pelvis and lower extremity		
Lower gastrointestinal	12	1.8
Prostate	35	5.3
Bladder	22	3.3
Oligometastases	17	2.6
Extremity	2	0.3
H&N and brain		
H&N	14	2.1
CNS	3	0.5
Thorax		
Lung and mediastinum	67	10.1
Oesophagus	3	0.5
Oligometastases	3	0.5
Bone	4	0.6
Breast		
APBI	203	30.5
WBRT	6	0.9
Patient volume by year		
2014	86	12.9
2015	163	24.5
2016	166	24.9
2017	211	31.7

H&N, head and neck; APBI, accelerated partial breast irradiation; WBRT, whole-brain radiotherapy

Table 2.

Selection of key institutional clinical protocols evaluating indications for and advantages of magnetic resonance image-guided radiotherapy (MRIgRT).

Study name	Investigational question	Hypothesised advantage of MRIgRT	Status	Primary result
MRIgRT for External Beam Accelerated Partial Breast Irradiation: Evaluation of Delivered Dose and Intrafractional Cavity motion	To determine the intrafractional motion of the breast surgical cavity and evaluate delivered versus planned dose	MRIgRT will demonstrate minimal intra-fraction motion with good tracking such that PTV margins can be reduced	Completed and published (Aacharya and Fischer-Valuck <i>et al.</i> , IJROBP 2016)	Median PTV volume could be reduced by 52% and dosimetric uncertainty was less than 1%
Phase I Trial of Stereotactic MR-guided Online Adaptive Therapy (SMART) for the Treatment of Oligometastatic or Unresectable Malignancies of the Abdomen	To evaluate the feasibility and safety of SMART for delivery of ablative radiation therapy to the abdomen	Online adaptive SBRT will be feasible and increase the therapeutic index of SMART	Completed and published (Henke <i>et al.</i> , IJROBP 2017)	SMART was clinically deliverable, resulted in zero grade 3 or greater CTCAE v4 acute toxicities, and increased the dosimetric therapeutic index in a majority of cases
Prospective Phase I study of Nab-Paclitaxel Plus Gemcitabine with Concurrent MR-guided IMRT in Patients with Locally Advanced or borderline resectable pancreatic cancer	Determination of the maximum tolerated dose level of hypofractionated (15 fx) with secondary end points of conversion to resectable disease and survival metrics	MRIgRT will improve the therapeutic index of radiation, such that it can be safely delivered concurrently with full-dose systemic therapy	Accruing at highest dose level of 67.5 Gy/15 fx + gemcitabine 1,000 mg/m ² and nab-paclitaxel 100 mg/m ²	Pending accrual completion
Evaluation of Single Fraction High-gradient Partial Breast Irradiation as the Sole Method of Radiation Therapy for Low To risk Stage 0 and I Breast Carcinoma	To quantify the tolerance by estimating rates of acute and late CTCAE v4 grade 3+ toxicities and estimate the ipsilateral breast recurrence rate 5 years post-treatment	Single fraction APBI will result in dosimetrically acceptable plans to deliver single fraction treatment for minimal impact of therapy on quality of life, low toxicity, and good cosmetic outcomes	Accrual completed.	Preliminary toxicity results reported at ASTRO 2017 (Zoberi <i>et al.</i>), with zero CTCAE v. 4 Grade 2+ acute toxicities observed; preliminary cosmetic results to be presented at ASTRO 2018
Prospective phase II study of Stereotactic (daily) Adapted MR-guided Radiation Therapy (SMART) for Patients with Borderline or Inoperable Locally Advanced Pancreatic Cancer	To determine the 90-day rates of CTCAE v.4 Grade 3 or higher gastrointestinal toxicity and to evaluate long-term survival metrics	MRIgRT will permit escalated dose and result in reduced acute GI toxicity compared to historical controls. MRIgRT will result in improved survival outcomes compared to historical controls	Not yet open to accrual	Pending accrual completion

PTV, planning target volume; IMRT, intensity modulated radiotherapy; IROBP, International Journal of Radiation Oncology, Biology, and Physics; ASTRO, American Society for Radiation Oncology; APBI, accelerated partial breast irradiation; fx, fraction; CTCAE v4, Common Terminology Criteria for Adverse Events version 4.