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Original Research Article

Multi-institutional experience of MR-guided stereotactic body radiation therapy for adrenal gland metastases

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ABSTRACT

Purpose: While dose escalation is associated with improved local control (LC) for adrenal gland metastases (AGMs), the proximity of gastrointestinal (GI) organs-at-risk (OARs) limits the dose that can be safely prescribed via CT-based stereotactic body radiation therapy (SBRT). The advantages of magnetic resonance-guided SBRT (MRgSBRT), including tumor tracking and online plan adaptation, facilitate safe dose escalation.

Methods: This is a multi-institutional review of 57 consecutive patients who received MRgSBRT on a 0.35-T MR linac to 61 AGMs from 2019 to 2021. The Kaplan-Meier method was used to estimate overall survival (OS), progression-free survival (PFS), and LC, and the Cox proportional hazards model was utilized for univariate analysis (UVA).

Results: Median follow up from MRgSBRT was 16.4 months (range [R]: 1.1–39 months). Median age was 67 years (R: 28–84 years). Primary histologies included non-small cell lung cancer (N = 38), renal cell carcinoma (N = 6), and melanoma (N = 5), amongst others. The median maximum diameter was 2.7 cm (R: 0.6–7.6 cm), and most AGMs were left-sided (N = 32). The median dose was 50 Gy (R: 30–60 Gy) in 5–10 fractions with a median BED_{10} of 100 Gy (R: 48–132 Gy). 45 cases (74 %) required adaptation for at least 1 fraction (median: 4 fractions, R: 0–10). Left-sided AGMs required adaptation in at least 1 fraction more frequently than right-sided AGMs (88 % vs 59 %, $p = 0.018$). There were 3 cases of reirradiation, including 60 Gy in 10 fractions (N = 1) and 40 Gy in 5 fractions (N = 2). One-year LC, PFS, and OS were 92 %, 52 %, and 78 %, respectively. On UVA, melanoma histology predicted for inferior 1-year LC (80 % vs 93 %, $p = 0.012$). There were no instances of grade 3+ toxicity.

Conclusions: We demonstrate that MRgSBRT achieves favorable early LC and no grade 3 + toxicity despite prescribing a median BED_{10} of 100 Gy to targets near GI OARs.

1. Introduction

The adrenal gland is a relatively common site of metastatic disease for several cancers, including primary tumors of the lung, breast, esophagus, stomach, liver, and malignant melanoma [1,2]. Though adrenal gland metastases (AGMs) can cause symptoms, most are diagnosed incidentally during routine surveillance imaging [2]. Historically, local therapies such as surgical resection or external beam radiotherapy (EBRT) were reserved for patients with symptomatic AGMs. However, select patients with a limited number of metastases are increasingly considered for surgery or EBRT, as multiple recent trials have demonstrated a progression-free survival (PFS) and in some cases an overall survival (OS) benefit from the addition of local therapy to systemic therapy in the oligometastatic [3,4], oligoprogressive [5,6], or oligoresidual [7] settings.

Stereotactic body radiation therapy (SBRT) is well-established in the treatment of adrenal oligometastases [8–12]. Though a recent meta-analysis has established the importance of dose escalation

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(biologically effective dose (BED_{10}) ≥100 Gy) in SBRT of AGMs in improving local control (LC), the proximity of mobile gastrointestinal (GI) organs-at-risk (OARs) often limits the dose that can be safely delivered using computed tomography (CT) image guidance [13]. Magnetic resonance-guided SBRT (MRgSBRT) has several unique advantages including real-time intrafraction tumor tracking, improved soft tissue visualization, and online plan adaptation, that can increase the precision of SBRT and allow for safe dose escalation [14–17]. Given the limited experience with dose-escalated SBRT in this specific setting, we hypothesized that MRgSBRT for the treatment of AGMs would facilitate safe and effective delivery of ablative dose delivery as assessed across multiple institutions.

2. Materials and methods

2.1. Patient population

This is a multi-institutional retrospective review of 57 consecutive patients who underwent MRgSBRT on a 0.35-Tesla (T) MR linac to 61 AGMs from April 2019 to September 2021. The study was approved by the institutional review boards at each respective institution contributing data to the multi-institutional dataset with corresponding data transfer agreements. Patients with a histologic confirmation of cancer and evidence of AGMs treated with MRgSBRT met the inclusion criteria. Within oligometastatic disease, cases were classified per ESTRO/EORTC guidelines (Table 1) [18].

2.2. Stereotactic body radiation therapy

Patients underwent MR simulation on the 0.35T MR-linac (ViewRay, Inc., Denver, CO) with a balanced steady-state free progression (True-FISP) imaging sequence, as described previously [19]. Patients were simulated in the supine position without an immobilization device using both deep inspiratory breath hold (DIBH) and free breathing techniques. Patients were asked to have nothing by mouth 2–3 h prior to simulation. A representative slice of the lesion was contoured as a tracking structure on a single-plane sagittal cine MRI sequence at 4 or 8 frames per second, and a 3 mm gating structure was created for treatment delivery. Patients then underwent a breath-hold CT simulation for electron density data in the same position.

Gross tumor volume (GTV) delineation was performed by the radiation oncologist utilizing the MR planning scan. A uniform 3–5 mm expansion of the GTV was utilized to create the planning target volume (PTV). Doses were prescribed to the 95 % isodose line. Per the treating radiation oncologist discretion, various dose-painting methods were utilized in 18 treatment plans (29.5 %), in which the GTV received a simultaneous integrated boost to a higher dose than the PTV. In these cases, the highest dose received was used to calculate the BED (assuming $\alpha/\beta = 10$).

OAR delineation included the stomach, duodenum, large bowel, small bowel, liver, spinal cord, and kidneys. Planning OAR volumes (PRVs) were created using a 3 mm margin for GI OARs. Patients were treated either on consecutive days or on alternating days with MRgSBRT, and prior to treatment delivery, patients underwent an MRI scan on the MR-linac. The treating physician made the decision of whether to adapt the treatment plan based upon predicted target coverage, OAR constraints, and dose distribution. In general, the dose constraints utilized for 5-fraction SBRT regimen included the following: spinal cord maximum dose <20–30 Gy, bowel, duodenum, and stomach maximum dose ≤38 Gy and dose to 0.5 cc ≤ 33–35 Gy, kidney mean dose <8–10 Gy, and at least 30 % of the liver volume receiving <10 Gy or at least 700 cc of liver receiving ≤21 Gy. However, dose constraints were at times customized for each patient as deemed appropriate byte treating physician.

The adaptive process was performed as previously described [20,21]. The patient was aligned with daily image (MR-guidance). After appropriate alignment, an "OAR eval" structure was used (PTV expanded 2 cm sup/inf and 3 cm radially) and the OARs within this structure are recontoured daily for adaptive treatment. The original radiotherapy plan was applied to the anatomy of the day and dose predicted to the critical OARs and tumor. Pre-specified OAR constraint violations (and/or tumor coverage) triggered adaptation if violated by the original radiotherapy plan. If a new radiotherapy plan was decided on, this went through a secondary QA check (gamma analysis) before delivery with a 2 % dose error threshold, 2 mm distance-to-agreement threshold and 10 % maximum dose analysis cut off threshold.

Table 1
Patient and Tumor Characteristics.

Variable	*n*	*%*
Age at time of SBRT (years)		
Median (range)	67 (28–84)	
Gender		
Female	26	45.6 %
Male	31	54.4 %
KPS		
90–100	33	57.9 %
70–80	22	38.6 %
60	2	3.5 %
Stage at Original Diagnosis		
I	7	12.3 %
II	5	8.8 %
III	18	31.6 %
IV	27	47.4 %
Primary Histology		
NSCLC	38	66.7 %
RCC	6	10.5 %
Melanoma	5	8.8 %
SCLC	3	5.3 %
Breast IDC	2	3.5 %
Angiosarcoma	1	1.8 %
Rectal Adenocarcinoma	1	1.8 %
Esophageal Adenocarcinoma	1	1.8 %
Prostate Adenocarcinoma	1	1.8 %
Bladder UCC	1	1.8 %
Merkel Cell Carcinoma	1	1.8 %
Cutaneous SCC	1	1.8 %
Oligometastatic Classification		
Synchronous Oligometastatic	4	6.7 %
Metachronous Oligorecurrence	12	20.0 %
Metachronous Oligoprogression	5	8.3 %
Repeat Oligorecurrence	5	8.3 %
Repeat Oligoprogression	19	31.7 %
Repeat Oligopersistence	2	3.3 %
Induced Oligoprogression	8	13.3 %
Induced Oligopersistence	2	3.3 %
Laterality		
Right	29	47.5 %
Left	32	52.5 %
GTV (cc)		
Median (range)	22.6 (1.1–297)	
Pretreatment maximum diameter (cm)		
Median (range)	2.7 (0.6–7.6)	

Abbreviations: No. = number, SBRT = stereotactic body radiation therapy, KPS = Karnofsky performance status, NSCLC = non-small cell lung cancer, RCC = renal cell carcinoma, SCLC = small cell lung cancer, IDC = invasive ductal carcinoma, UCC = urothelial cell carcinoma, SCC = squamous cell carcinoma.

2.3. Response evaluation and follow-up

All patients were evaluated for acute toxicity on a weekly basis during treatment. Patients were seen in follow up every 3 to 6 months following treatment. Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. For 60 of the 61 treatments, there was available imaging for response evaluation at least 3 months after treatment. Unrelated to treatment, one patient expired shortly following SBRT, and therefore, did not have post-treatment imaging for response evaluation. For the 24 cases with available positron emission tomography (PET) scans, tumor response was determined using the PET Response Evaluation Criteria in Solid Tumors (PERCIST), version 1.0 [22]. For the 60 cases with available computed tomography (CT) scans, tumor response was determined using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [23]. Overall response rate (ORR) was defined as the proportion of patients who had a complete or partial response.

2.4. Statistical analysis

The Kaplan-Meier (KM) method was used to estimate time-to-event outcomes measured from the end of MRgSBRT, including OS, LC, and PFS. The Cox proportional hazards model was utilized for univariate analysis of OS, LC, and PFS. Two-tailed p values < 0.05 were considered to indicate statistical significance. Statistical analyses were performed using JMP 15 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Patient, tumor, and treatment characteristics

The median age for the cohort was 67 years (range: 28–84 years), and primary histologies included non-small cell lung cancer (NSCLC, N = 38), renal cell carcinoma (RCC, N = 6), and melanoma (N = 5), amongst others (Table 1). The median maximum diameter was 2.7 cm (R: 0.6–7.6 cm), and most AGMs were left-sided (N = 32). Patients received MRgSBRT to a median dose of 50 Gy (range: 30–60 Gy) in 5–10 fractions with a median BED_{10} of 100 Gy (range: 48–132 Gy, interquartile range 96–100 Gy, Table 2). Most patients (61 %) had received prior immunotherapy, and concurrent immunotherapy was utilized in 16 cases (26 %). There were 5 patients with NSCLC who had received prior epidermal growth factor receptor (EGFR) inhibition and 4 patients with melanoma who had received prior B-type Raf kinase (BRAF)/mitogen-activated protein kinase (MEK) inhibition. There were 3 cases of reirradiation. One patient received 60 Gy in 10 fractions after receiving 35 Gy in 5 fractions 8 months prior. Two patients received 40 Gy in 5 fractions after originally undergoing 37.5 Gy in 15 fractions 4 years prior and 60 Gy in 5 fractions 6 years prior.

Of the 61 treated AGMs, 45 cases (74 %) required online adaptation for at least 1 fraction (median: 4 fractions, range 0–10 fractions), and in 29 cases (48 %), online adaption was required in all treated fractions. Of the 310 total MRgSBRT fractions, 199 (64 %) required adaption. The indications for adaptation were OAR sparing in all cases and improving target coverage in 38 %. The BED_{10} did not significantly vary between cases requiring adaptation and those that did not ($p = 0.459$). Left-sided AGMs required adaptation in at least 1 fraction more frequently than right-sided AGMs (88 % vs 59 %, $p = 0.018$), and 65 % of left-sided AGMs required adaptation for all fractions.

3.2. Clinical outcomes

Median follow up from SBRT was 16.4 months (range: 1.1–39 months). The ORR was 45 % per RECIST criteria and 67 % per PERCIST criteria (Table 2). One-year LC, PFS, and OS were 92 % (95 % CI: 81–97 %), 52 % (95 % CI: 39–65 %), and 78 % (95 % CI: 65–87 %), respectively (Fig. 1A–C). On UVA, melanoma histology predicted for inferior 1-year

Table 2
Treatment Characteristics.

Variable	*n*	*%*
Prior Local Therapy		
None	56	91.8 %
XRT	3	4.9 %
Adrenalectomy	2	3.3 %
Prior Immunotherapy		
Yes	37	60.7 %
No	24	39.3 %
Prior EGFR Inhibitor		
Yes	5	8.2 %
No	56	91.8 %
Prior BRAF/MEK Inhibitor		
Yes	4	6.6 %
No	57	93.4 %
Concurrent Immunotherapy		
Yes	16	26.2 %
No	45	73.8 %
Reirradiation		
Yes	3	4.9 %
No	58	95.1 %
Radiation Fractionation Scheme		
60 Gy in 5 fractions	13	21.3 %
50 Gy in 5 fractions	32	52.5 %
60 Gy in 10 fractions	1	1.6 %
45 Gy in 5 fractions	2	3.3 %
40 Gy in 5 fractions	11	18.0 %
35 Gy in 5 fractions	1	1.6 %
30 Gy in 5 fractions	1	1.6 %
BED_{10} (Gy)		
132	13	21.3 %
100	32	52.5 %
96	1	1.6 %
85.5	2	3.3 %
72	11	18.0 %
59.5	1	1.6 %
48	1	1.6 %
Percentage of Adapted Fractions		
0 %	16	26.2 %
20 %	2	3.3 %
40 %	2	3.3 %
60 %	5	8.2 %
80 %	7	11.5 %
100 %	29	47.5 %
Reasons for Adaptation		
OAR	22	48.9 %
Target and OAR	23	51.1 %
Response per RECIST		
CR	2	3.3 %
PR	25	41.0 %
SD	32	52.5 %
PD	1	1.6 %
NA	1	1.6 %
Response per PERCIST		
CMR	9	14.8 %
PMR	7	11.5 %
SMD	7	11.5 %
PMD	1	1.6 %
NA	37	60.7 %

Abbreviations: XRT = external radiation therapy, BED_{10} = biologically effective dose assuming $\alpha/\beta = 10$, OAR = organ-at-risk, RECIST = response evaluation

criteria in solid tumors, PERCIST = positron emission tomography response criteria in solid tumors.

LC (80 % vs 93 %, $p = 0.012$, Table 3). Inferior Karnofsky score was also predictive for inferior LC. The BED_{10} prescribed, pretreatment size, and laterality of the AGM did not predict for LC. On UVA, reirradiation cases were predictive of inferior PFS (HR 3.55, $p = 0.042$). The Karnofsky performance score was the only predictor of OS.

Of the 57 patients who underwent SBRT, 20 patients (35 %) experienced grade 1 acute toxicity and 4 patients (7 %) experienced grade 2 acute toxicity, including fatigue, nausea/vomiting, and abdominal pain (Supplemental Table 1). There were no instances of grade 3+ acute or late toxicity.

4. Discussion

Though SBRT has emerged as a relatively safe, non-invasive, and effective treatment for AGMs, LC following SBRT is quite variable and significantly influenced by dose (1-year LC 66–100 %) [8–13,24–28]. However, the proximity of GI OARs often limits the SBRT dose that can be safely prescribed to an AGM, particularly on the left side due to the stomach, large, and small bowel. There are several advantages of MRgSBRT, including improved soft tissue visualization, real time intrafraction tumor tracking, and online plan adaptation, that facilitate safe dose escalation in the treatment of AGMs. In the largest, multi-institutional experience to date, we demonstrate MRgSBRT to be a safe and effective treatment for AGM, with favorable LC and low rates of acute and late toxicity despite a relatively high median BED_{10}.

Following MRgSBRT to a median BED_{10} of 100 Gy (range 48–132 Gy), we demonstrate a 1-year LC rate of 92 % (Fig. 1A), which compares favorably to the literature (66–100 %) [8–13,24–28]. Though the present study did not demonstrate a significant effect of SBRT dose upon LC, this was likely due to a limited sample size and limited BED variations, as multiple prior studies have found increased dose predictive of improved LC [13,25,26]. In a retrospective review of 49 AGM treated with CT-guided SBRT, Chance et al. found no instances of local failure in cases treated with doses above a BED_{10} of 100 Gy [26]. In another study of 149 AGM treated with CT-guided SBRT, Scorsetti et al found that BED_{10} was an independent predictor of LC [25]. In a large meta-analysis including 1006 patients with AGM treated with CT-guided SBRT to a median BED_{10} of 67 Gy, Chen et al. found a strong association between BED_{10} and LC, as a BED_{10} of 60 Gy, 80 Gy, and 100 Gy predicted 1-year LC of 71 %, 85 %, and 93 %, respectively [13]. Although the experience is limited, the median doses prescribed in studies of MRgSBRT for AGM, including the present study, are relatively high (median BED_{10} 89.6–100 Gy) [17,29–31], which likely contributes to the favorable 1-year LC rates demonstrated by these studies (92–100 %) [17,31]. These data indicate that dose escalation is an important determinant of LC, and with the improved precision due to intrafraction tumor tracking and online plan adaptation, physicians may feel more comfortable prescribing higher doses with MRgSBRT as compared with CT-guided techniques.

The primary histology of the oligometastasis is another important factor that can influence LC after SBRT. Prior studies have established that the radiosensitivity of liver [32] and lung metastases [33] varies significantly by primary tumor histology. Radioresistant primary histologies, such as colorectal cancer, melanoma, RCC, and soft tissue sarcoma, tend to have radioresistant metastases that are at higher risk for local failure following SBRT. Indeed, studies have confirmed that patients with these histologies experience higher rates local failure after radiotherapy to brain [34], spine [35], liver [32], and lung [33] oligometastases. In the present study, we found concordant results, as patients with melanoma were at a greater risk of local failure (Table 3). Our data suggests that similar to liver, lung, spine, and brain metastases, melanoma AGMs may be more radioresistant than other histologic subtypes, and therefore, dose escalation may be warranted in these cases

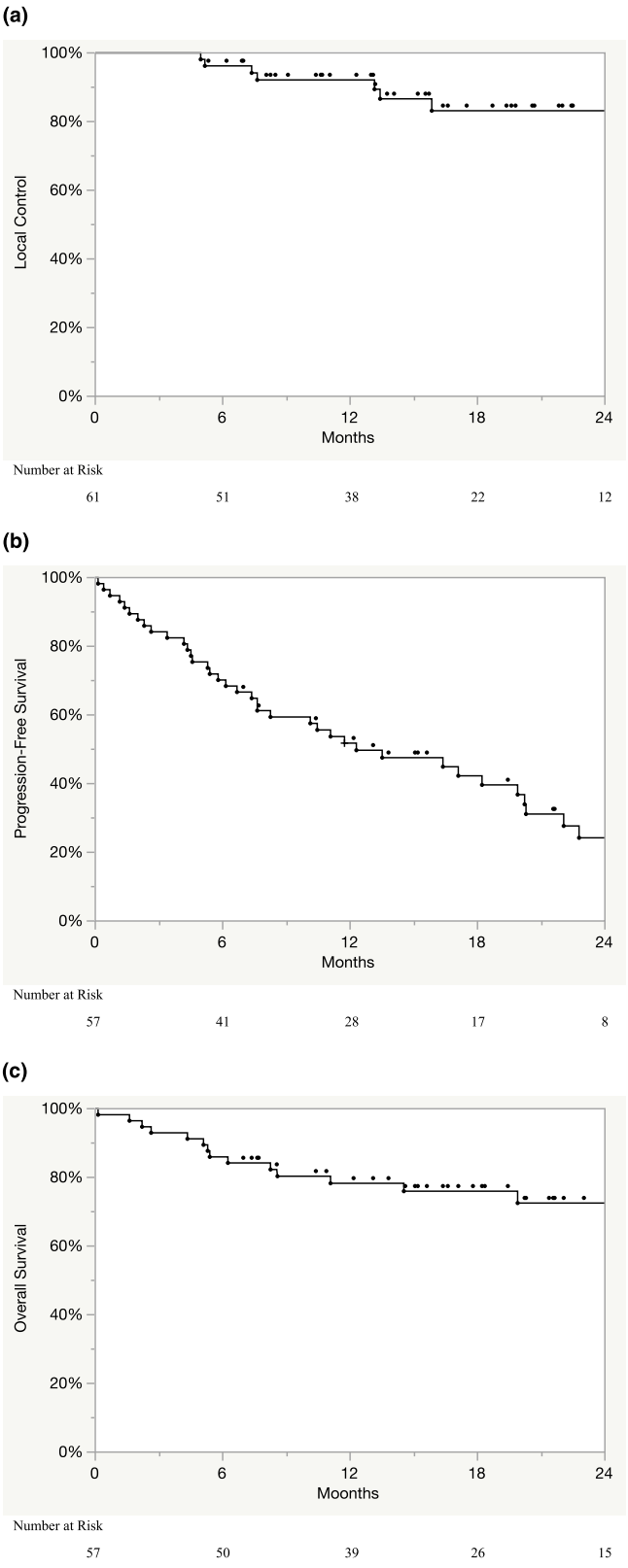

Fig. 1. Kaplan-Meier curves for (A) local control, (B) progression-free survival, and (C) overall survival for patients with adrenal gland metastases treated with magnetic resonance-guided stereotactic body radiation therapy.

Table 3
Univariate analysis for LC, PFS, and OS.

	Local Control		Progression-Free Survival		Overall Survival	
Variable	*HR*	*p value*	*HR*	*p value*	*HR*	*p value*
Age at SBRT	0.99 (0.93–1.07)	0.757	1.00 (0.97–1.04)	0.776	1.01 (0.96–1.06)	0.801
Gender						
Female (Reference)	1.00	–	1.00	–	1.00	–
Male	2.16 (0.42–11.1)	0.358	1.17 (0.61–2.23)	0.633	0.95 (0.35–2.57)	0.914
KPS						
90–100 (Reference)	1.00	–	1.00	–	1.00	–
70–80	5.49 (1.06–28.5)	**0.043**	1.90 (0.98–3.68)	0.059	4.01 (1.31–12.2)	**0.015**
60	–	–	3.37 (0.76–14.9)	0.109	11.8 (2.14–65.2)	**0.005**
Oligometastatic Classification						
De-novo OMD (Reference)	1.00	–	1.00	–	1.00	–
Repeat OMD	0.45 (0.07–2.70)	0.381	1.15 (0.56–2.35)	0.706	1.03 (0.30–3.57)	0.965
Induced OMD	1.64 (0.27–9.84)	0.591	1.44 (0.57–3.62)	0.439	2.76 (0.74–10.3)	0.131
Histology						
Non-melanoma (Reference)	1.00	–	1.00	–	1.00	–
Melanoma	6.82 (1.52–30.6)	**0.012**	1.60 (0.62–4.12)	0.326	–	–
Laterality						
Right (Reference)	1.00	–	1.00	–	1.00	–
Left	2.42 (0.47–12.5)	0.293	1.16 (0.61–2.19)	0.653	0.76 (0.28–2.05)	0.589
Pretreatment Maximum Diameter (cm)	0.72 (0.33–1.34)	0.328	1.03 (0.82–1.28)	0.796	1.32 (0.95–1.77)	0.328
Reirradiation						
No (Reference)	1.00	–	1.00	–	1.00	–
Yes	4.38 (0.48–39.6)	0.189	3.55 (1.05–12.0)	**0.042**	1.14 (0.15–8.64)	0.902
BED_{10} (Gy)	0.99 (0.96–1.02)	0.587	1.01 (099–1.02)	0.993	1.00 (0.98–1.02)	0.933

Abbreviations: LC = local control, PFS = progression-free survival, OS = overall survival, HR = hazards ratio, SBRT = stereotactic body radiation therapy, KPS = Karnofsky performance score, OMD = oligometastatic disease, BED_{10} = biologically effective dose assuming $\alpha/\beta = 10$.

to optimize LC.

Although dose escalation is important for improving LC, especially for radioresistant histologies, increasing dose increases the risk of toxicity of AGM SBRT due to the proximity of GI OARs. Overall, the risk of grade 3+ toxicity following AGM SBRT is low (1.8 %) [13]. However, there have been multiple reports of significant late toxicity following high dose CT-guided SBRT to left-sided AGMs. In a retrospective review of 10 patients with AGM treated with CT-guided SBRT, Plichta et al. reported a single case of GI bleed which occurred 3 months following SBRT to 45 Gy in 3 fractions (BED_{10} 112 Gy) of a left AGM [36]. A recent study of 27 patients with AGM treated with CT-guided SBRT reported 1 case of a late grade 5 posterior wall gastric ulcer which occurred 3 months after SBRT to the left adrenal gland [11]. The maximum dose to the stomach was 54.8 Gy delivered in 4 fractions. Onishi et al. reported a similar case of a patient who developed a fatal posterior stomach wall ulceration which occurred 3 months following CT-guided SBRT of 60 Gy in 10 fractions (BED_{10} 96 Gy) with concurrent vinorelbine to a left AGM [37]. A variety of SBRT techniques were utilized in these 3 studies, including generation of an internal target volume (ITV) from 4-D CT scans, respiratory gating, and treatment under breath hold. However, in contrast to the present study, none of these 3 studies utilized any adaptive planning. Despite a relatively high prescribed dose (median BED_{10} 100 Gy), no instances of grade 3+ toxicity occurred following MRgSBRT in the present study, which is consistent with the AGM MRgSBRT literature [17,38]. Since the majority of cases in the present study (74 %) required adaptive planning to meet OAR constraints for at least one fraction, it is likely that this feature of MRgSBRT reduced the risk of toxicity. Additionally, it is important to note that the fractionation schemes utilized were at the discretion of the radiation oncologist and varied by the risk of toxicity, with lower BED_{10} likely utilized for cases involving targets nearby OARs or cases of reirradiation, further contributing to the low rate of significant toxicity within the present study.

While comparison of clinical outcomes between CT-guided and MRgSBRT for AGM is limited by significant tumor and treatment heterogeneity within the literature, as well as a limited published MRgSBRT experience, multiple studies have demonstrated significant dosimetric advantages of MRgSBRT. Studies have found significant volume and positional changes during the course of AGM SBRT for the GTV [30,39] and nearby OARs [15,29]. This variability has significant implications for the treatment plan, as a majority of fractions in the present study (64 %) required adaption to meet OAR constraints and/or target coverage goals, which is consistent with the literature (69–99 %) [16,17,38]. MRgSBRT adapted plans have been shown to significantly improve PTV coverage and reduce the dose to OARs [14,17,29,38]. Rodriguez et al. conducted an analysis of 20 patients with AGM who underwent adaptive MRgRT who were replanned for volumetric modulated arc therapy (VMAT) CT-image guided radiation therapy (IGRT) [16]. Even when a breath-hold technique was utilized for the CT IGRT plans, there was a 72 % frequency of predicted indications for adaptation, and CT IGRT plans were nearly 3 times more likely to experience target coverage reduction compared with MRgRT. Although larger studies with longer follow up are required to confirm that these dosimetric advantages translate to significant improvements in clinical outcomes, these data suggest that MRgSBRT may provide improved LC with a reduced risk of toxicity in the treatment of AGM.

The present study has several important limitations. Firstly, the results are limited by the study's non-randomized, retrospective nature that causes an opportunity for selection bias. Additionally, there was significant heterogeneity of tumor characteristics, particularly for histology. There was also significant heterogeneity within the various treatment dose and fractionation regimens utilized. There was a relatively small sample size which likely limited the statistical analysis, and this may have contributed to the lack of an association between

reirradiation and LC, as well as the association of reirradiation and PFS. There was a limited follow up that limited our evaluation of the risk of long-term toxicity following SBRT for AGM. Despite these limitations, the multi-institutional component of this study showing consistent results across institutional practices shows that MRgSBRT for AGM is safe and effective. Most importantly, MRgSBRT appears to be most beneficial for left AGM to spare critical OARs.

5. Conclusions

Our results demonstrate that MRgSBRT of AGM achieves favorable LC with a low risk of significant acute toxicity despite prescribing a median BED_{10} of 100 Gy to targets in proximity of GI OARs. The unique advantages of MR guidance and online adaptive replanning may be especially advantageous for safe dose escalation of radioresistant histologies such as melanoma.

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Patient consent statement

This study was approved by the institutional review boards at each respective institution contributing data to the multi-institutional dataset with corresponding data transfer agreements. Patient consent was not deemed necessary due to the retrospective nature of this study.

CRediT authorship contribution statement

Matthew Mills: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Rupesh Kotecha:** Conceptualization, Writing – review & editing. **Roberto Herrera:** Data curation, Writing – review & editing. **Tugce Kutuk:** Data curation, Writing – review & editing. **Matthew Fahey:** Data curation, Writing – review & editing. **Evan Wuthrick:** Writing – review & editing. **G. Daniel Grass:** Writing – review & editing. **Sarah Hoffe:** Writing – review & editing. **Jessica Frakes:** Writing – review & editing. **Michael D. Chuong:** Conceptualization, Writing – review & editing. **Stephen A. Rosenberg:** Conceptualization, Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Rupesh Kotecha has received personal fees from Accuray Inc., Elekta AB, ViewRay Inc., Novocure Inc., Elsevier Inc., Brainlab, Kazia Therapeutics, Castle Biosciences, and institutional research funding from Medtronic Inc., Blue Earth Diagnostics Ltd., Novocure Inc., GT Medical Technologies, AstraZeneca, Exelixis, ViewRay Inc., Brainlab, Cantex Pharmaceuticals, and Kazia Therapeutics. Tugce Kutuk has received a travel stipend from GT Medical Technologies, Inc. Sarah Hoffe has received research funding from ViewRay, Inc, and Galera Pharmaceuticals. Jessica Frakes has received consulting fees from ViewRay, Inc, and a speaker bureau role for Boston Scientific. Evan Wuthrick has received consulting fees from ViewRay, Inc, AlphaTau, Castle, and Varian. Michael Chuong has received personal fees from ViewRay, Sirtex, IBA and institutional research funding from Novocure, ViewRay, and StratPharma. Stephen Rosenberg has received consulting fees and research support from Viewray, Inc., as well as consulting fees and speaker's honoraria from Novocure, Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100719.

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